Decreased Resting-State Activity in the Precuneus Is Associated With Depressive Episodes in Recurrent Depression

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ABSTRACT

Objective: To investigate alterations in resting-state spontaneous brain activity in patients with major depressive disorder (MDD) experiencing multiple episodes.

Methods: Between May 2007 and September 2014, 24 recurrent and 22 remitted patients diagnosed with MDD with the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I), and 69 healthy controls matched for age, sex, and educational level participated in this study. Among them, 1 healthy control was excluded due to excessive head motion. The fractional amplitude of low-frequency fluctuation (fALFF) was assessed for all recruited subjects during the completion of resting-state functional magnetic resonance imaging. Relationships between fALFF and clinical measurements, including number of depressive episodes and illness duration, were examined.

Results: Compared to patients with remitted MDD and to healthy controls, patients with recurrent MDD exhibited decreased fALFF in the right posterior insula and right precuneus and increased fALFF in the left ventral anterior cingulate cortex. Decreased fALFF in the right precuneus and increased fALFF in the right middle insula were correlated with the number of depressive episodes in the recurrent MDD groups ($r = -0.75$, $P < .01$ and $r = 0.78$, $P < .01$, respectively) and remitted MDD groups ($r = -0.63$, $P < .01$ and $r = 0.41$, $P = .03$, respectively). In addition to regions in the default mode network (DMN) and salience network, the altered resting-state activity in the middle temporal and visual cortices was also identified.

Conclusions: Altered resting-state activity was observed across several neural networks in patients with recurrent MDD. Consistent with the emerging theory that altered DMN activity is a risk factor for depression relapses, the association between reduced fALFF in the right precuneus and number of depressive episodes supports the role of the DMN in the pathology of recurrent depression.

J Clin Psychiatry 2017;78(4):e372–e382
https://doi.org/10.4088/JCP.15m10022

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Major depressive disorder (MDD) is a chronic, highly recurrent, debilitating psychiatric disorder that is associated with a high lifetime prevalence of 15%–30%.[1–3] Among patients who have remitted from a depressive state, 70% will develop new depressive episodes within 18 months.[4–6] More importantly, a high number of previous episodes were correlated with an increased risk for a depressive episode relapse.[7–9] As the number of depressive episodes increases, deficits in neural systems related to depression become increasingly severe, which may increase the sensitivity of patients with depression to even mild stressors. For instance, Jacobs et al[10] demonstrated that the burden of multiple episodes was related to hypoconnectivity of the left posterior cingulate cortex (PCC) to a number of cognitive control regions, including the bilateral inferior frontal gyrus and middle frontal gyrus. In addition, Nixon and colleagues[11] reported bilateral precuneus hypogyrification in recovered-state MDD patients with at least 2 previous episodes. Although each depressive episode may further damage the neural functions,[10,11] the consequence of depressive episode accumulation on neural functions has not been well studied.

Several hypotheses have been proposed in the literature regarding the neural mechanisms of depression.[12–16] The most consistent findings from previous neuroimaging studies were the impaired reciprocal functional interactions within the corticolimbic circuits,[12,17,18] particularly in the overactive ventral affective system (eg, amygdala, insula, ventral anterior cingulate cortex [ACC], and medial prefrontal cortex [mPFC]) and the inactive dorsal executive system (eg, hippocampus, dorsal ACC, posterior cingulate or precuneus, and dorsolateral prefrontal cortex).[13,19] Within the corticolimbic circuits, several midline regions (eg, ventral ACC, mPFC, and posterior cingulate/precuneus) were considered to belong to the default mode network (DMN).[20,21] More specifically, recent work also revealed the essential role of 3 networks—the DMN, salience network, and executive network—on mood disorders.[22] In particular, it was identified that changes in the relationships among these 3 core intrinsic connectivity networks were related to depressive symptoms, including rumination, emotional disinhibition, and emotional overreactivity.[22,23] However, it remains unknown which regions or networks are essential or specific to the relapse of depression.

Interestingly, early neuroimaging studies suggested that the DMN has been considered as a potential neural

Clinical Points

- The neural underpinnings of recurrent depression currently remain poorly understood.
- Depression–state-related alteration in resting-state activity was associated with the number of depressive episodes.
- Findings are consistent with the emerging theory that the altered default mode network is a risk factor for depression relapse.

substrate for ruminative thoughts and introspective cognitive patterns in MDD.[3,20,24–30]A recent review from Mulders et al[31] highlighted the hyperconnectivity between the anterior DMN and the salience network and the hypoconnectivity between the posterior DMN and the central executive network in MDD. Another meta-analysis from the work of Kaiser et al[32] showed the hyperconnectivity within the DMN in MDD. Despite growing evidences for the altered functional connectivity within the DMN in MDD, to date there is no systematic evidence for specific differences between recurrent MDD and remitted MDD. In addition, converging evidence suggested that the increased DMN activity is associated with internally focused appraisal.[33,34] For example, Nixon et al[11] observed that the task-based DMN hyperconnectivity during Go/No-Go performance was associated with hypogyrification of key DMN regions (eg, precuneus) in recovered-state MDD, supporting the DMN as a plausible substrate for the ruminative and introspective cognitive patterns of MDD. Further, it was also found that an overactive resting state in the mPFC region (the anterior node of the DMN) in treatment-naïve patients with MDD might be related to the recurrent tendency to rumination and deficits in the cognitive control in MDD.[28] On the basis of the previous findings, it is rational to suggest that the hyperconnectivity in the DMN (primarily the precuneus) acts as an essential substrate for dysregulation of the synchronized switch between internally and externally oriented attention in recovered-state MDD, which ultimately can cause the cognitive deficits, rumination, impaired attention control, cognitive reactivity. and biological-level vulnerability to recurrence.[5]

To validate these hypotheses, it is essential to explore whether spontaneous regional neuronal activity in the DMN prevails in patients with both depressive-state and remitted-state MDD. These hypotheses can be further validated if alterations in the DMN are related to the number of previous depressive episodes. Interestingly, the increased resting activity in the DMN has been identified in the mPFC, subgenual cingulate, and posterior cingulate or precuneus,[20,30,35] and a dominant task-negative over task-positive activity bias has also been manifested during the resting state in patients with depression.[36] However, it remains unclear whether these alterations are completely reversed in patients with remitted MDD. In contrast, Li et al[25] presented a distinction between metabolic rostral ACC impairments related to state markers and dorsal structural impairments related to traits that persisted during remission. However, their findings indicated only that both mechanisms could lead to abnormal functional responses. Importantly, the relationship between alterations in resting-state activity with mechanisms that discern features of acute recurrent depression versus persistent deficits during remission has never been examined in younger adults.

Due to its advantages of high resolution, no radiation, and easy application, resting-state functional magnetic resonance imaging (fMRI) has received extensive attention in the investigation of brain function underlying normal and different pathological conditions.[14,37,38] The resting state is typically defined as a nonspecific cognitive task during fMRI scanning[37] in which participants are instructed to remain still, close their eyes, think of nothing in particular, and try not to fall asleep. On the basis of functional neuroimaging studies, Raichle[38] proposed that resting-state activity can consume a large portion of brain energy. More recent studies[37,39,40] have reported that spontaneous activity can be investigated via a number of techniques, including functional connectivity, regional homogeneity, amplitude of low-frequency fluctuation (ALFF), and fractional ALFF (fALFF). Among these, ALFF and fALFF are considered to be related to field potential activity, and they can encode the intensity of spontaneous regional neuronal activity during the baseline state. One advantage of fALFF over ALFF is that fALFF is less sensitive to motion artifacts[41–43] and can thereby effectively reveal the cognitive-affective processes underlying various cognitive-affective disorders.[44,45] Therefore, fALFF reflects the relationship between local spontaneous brain alterations and cognitive-emotional processing in MDD. For the present study, we aim to capture and compare resting-state neural activity strength using fALFF among patients with recurrent MDD who are in an actively depressed state, patients with remitted MDD who are in a remitted state, and healthy controls. We will also examine the hypothesis that altered resting-state activity in the DMN (especially in the precuneus) is an essential biomarker for depression with multiple episodes and can be a depression–state-related marker as well.

METHODS

Participants

From May 2007 to September 2014, 24 recurrent MDD patients who were in an actively depressed state, 22 remitted MDD patients, and 69 healthy controls (HC) participated in this study. One HC was excluded due to excessive head motion. The protocol was approved by the Medical Ethics Committee of Beijing Anding Hospital, Capital Medical University, China. Participants were provided with an informed description of the study procedures, and all participants signed the informed consent forms before starting the experiments.

Patient diagnoses of remitted MDD and recurrent MDD were established by the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I) criteria.[46] All patients

Table 1. Group Demographics and Clinical Measures

Measure	Patients With Recurrent MDD (n = 24)	Patients With Remitted MDD (n = 22)	Healthy Controls (n = 68)	Statistical Value	*P* Value
Age, mean ± SD, y	37.62 ± 14.35	38.68 ± 12.52	35.60 ± 12.37	0.57	0.57[a]
Education level, mean ± SD, y	14.92 ± 3.25	14.41 ± 3.40	15.41 ± 4.00	0.64	0.53[a]
Sex (male/female)	10/14	8/14	34/34	1.44	0.49[b]
HDRS, mean ± SD	21.88 ± 4.61	4.68 ± 2.57		5.47	0.00[a]
HARS, mean ± SD	20.08 ± 7.46	5.77 ± 3.24		8.31	0.00[c]
Whole brain, mean ± SD	1,406 ± 117.4	1,380 ± 161.0	1,395 ± 131.2	0.22	0.80[a]
Duration of illness, mean ± SD, y	9.08 ± 10.24	9.23 ± 6.54		−0.06	0.96[c]
Number of depressive episodes, mean ± SD	3.41 ± 1.66	3.23 ± 1.77		0.37	0.71[c]
Number of patients taking specific drugs, n					
Antidepressants	24	20			
SSRI	16	14			
SNRI	5	2			
Trazodone	1	0			
TCA	0	3			
Flupentixol/melitracen tetracyclic	2	1			
Mood-stabilizer	1	1			
Valproic acid	1	0			
Carbamazepine	0	1			
Antipsychotics	2	6			
Quetiapine	2	2			
Risperidone	0	4			
Benzodiazepines	1	2			
Clonazepam	0	1			
Oxazepam	1	1			
Medication-free	2	0			

[a]*P* values for 1-way ANOVA. [b]χ^2 test. [c]*P* values for 2-sample *t* tests.
Abbreviations: ANOVA = analysis of variance, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, SD = standard deviation, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

met the following criteria: (1) between 18 and 60 years of age, (2) right-handed, (3) satisfied *DSM-IV*[47] criteria for MDD, (4) no history of neurologic or other chronic medical diseases, (5) no history of other psychiatric disorders such as schizophrenia or obsessive-compulsive disorder, (6) no history of stimulant use for MDD, and (7) no history of alcohol or substance abuse. The 17-item Hamilton Depression Rating Scale (HDRS)[48] and Hamilton Anxiety Rating Scale (HARS)[49] also were used to measure the severity of patient depression and anxiety, respectively, on the day of scanning.

Recurrence implies that the number of depressive episodes is ≥ 2. A depressive episode was determined based on the severity of clinical symptoms as measured by the HDRS.[48] A HDRS value ≥ 17 that persisted for at least 2 weeks was considered a new episode of depression. A HDRS score ≤ 7 that lasted for at least 2 weeks was considered remission.[2,50] Demographic and clinical measures are presented in Table 1. The HC also were screened by psychiatrists using the nonpatient version of the SCID, and those with a family history of major psychiatric disorders, including schizophrenia, major depressive disorder, bipolar disorder, or other Axis I psychiatric disorders in first-degree relatives, were excluded from the study.

Imaging Procedures

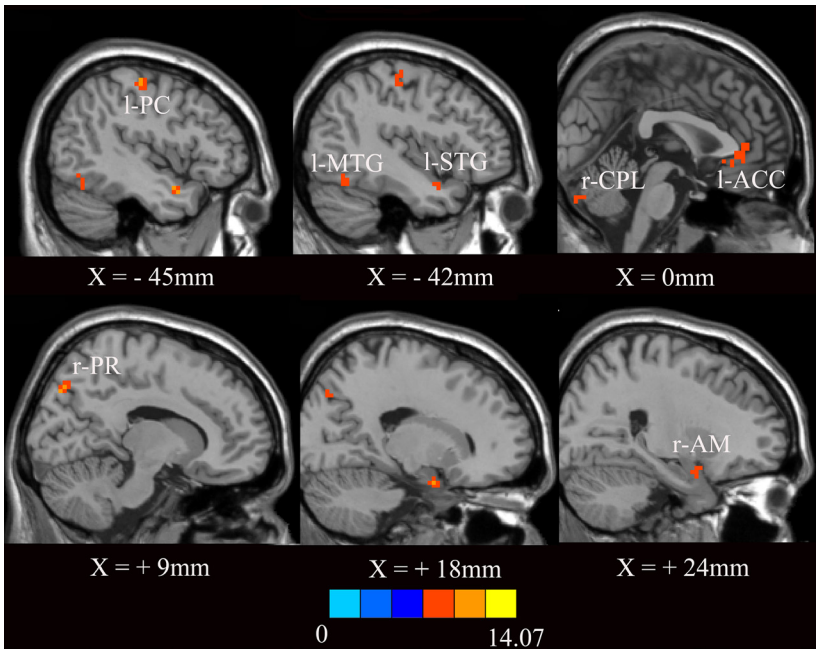
Images were acquired using a 3.0-Tesla MRI scanner (Siemens Medical Solutions, Erlangen, Germany) at the National Key Laboratory for Cognitive Neuroscience and Learning, Beijing Normal University. The parameters for resting-state fMRI were as follows: 33 axial slices, echo-planar imaging pulse sequence, thickness/gap = 3.5/0.6 mm, in-plane resolution = 64 × 64, repetition time (TR) = 2,000 milliseconds, echo time (TE) = 30 milliseconds, flip angle (FA) = 90°, field of view (FOV) = 220 × 220 mm, and 240 volumes. The participants were asked to relax with their eyes closed and think of nothing in particular during the entire resting-state fMRI scan. After the scanning was complete, a simple survey was administered to confirm that the patients had not fallen asleep. The parameters for 3D-T1 images were 128 sagittal slices, slice thickness/gap = 1.33/0 mm, in-plane resolution = 256 × 192, TR = 2,530 milliseconds, TE = 3.39 milliseconds, FOV = 256 × 256 mm, inversion time (TI) = 1,100 milliseconds, and FA = 7°.

Imaging Data Preprocessing

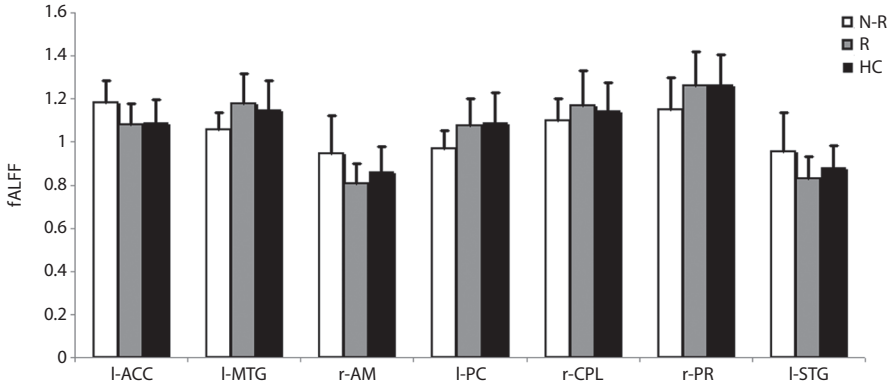
The first 10 volumes were discarded to isolate the signal equilibrium. Slice correction for acquisition delay and realignment for rigid body motion were then performed. Data from 1 HC were excluded from further processing due to excessive head motion (translation or rotation of more than 2 mm or more than 2°). Individual 3D structural images were segmented into gray matter images, which were spatially normalized to Montreal Neurologic Institute space (resampled voxel size = 3 × 3 × 3 mm^3). Resting-state fMRI data were then spatially smoothed by a Gaussian kernel with a full width at half-maximum equal to 4 mm. Finally, detrending was performed to remove the linear trend of

Figure 1. Differences in fALFF Values Within Brain Scans Among the 3 Groups

A. Differences in fALFF Values Within the Whole-Brain Mask Among the 3 Groups[a]



B. Mean fALFF Values in Each Region of Interest Among the 3 Groups[b]



[a]One-way ANOVA reveals differences in fALFF values within the whole-brain mask among the 3 groups (recurrent MDD, ie, nonremitted MDD [N-R]; remitted MDD [R]; and healthy controls [HC]) including age, sex, educational level, and whole-brain volume as covariates. The numbers below the images refer to the x-coordinates according to the Montreal Neurologic Institute atlas. The color bar represents the *F* value from ANOVA. The statistical threshold was set at $F < 4.817$ ($P < .01$) with cluster size > 486 mm^3 (18 voxels), corresponding to an AlphaSim corrected $P < .05$.

[b]ROI analysis used peak coordinates within a 5-mm radius for l-ACC, l-MTG, r-AM, l-PC, r-CPL, r-PR, and l-STG, respectively, from 1-way ANOVA.

Brain abbreviations: l-ACC = left anterior cingulate cortex, l-MTG = left middle temporal gyrus, l-PC = left postcentral gyrus, l-STG = left superior temporal gyrus, r-AM = right amygdala, r-CPL = right cerebellum posterior lobe, r-PR = right precuneus.

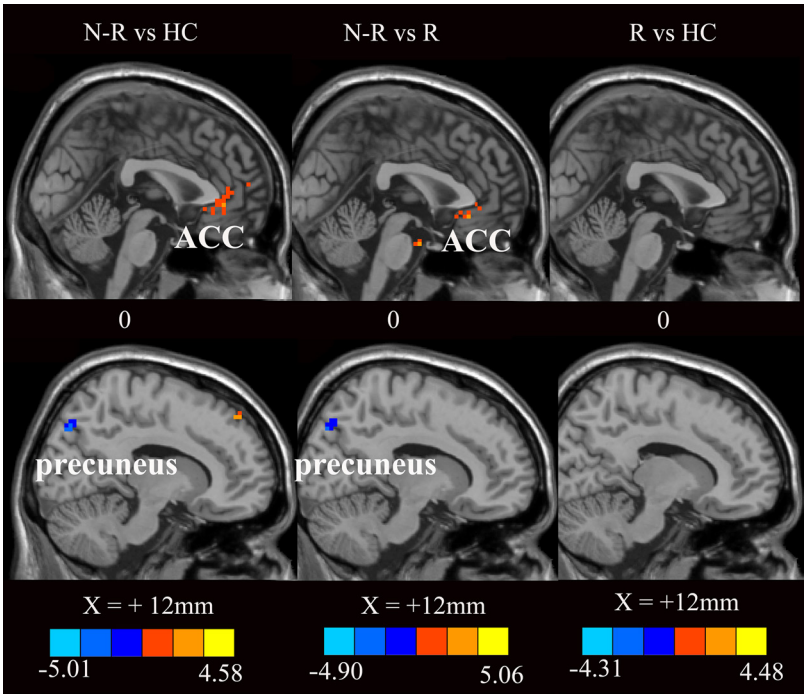
General abbreviations: ANOVA = analysis of variance, fALFF = fractional amplitude of low-frequency fluctuation, HC = healthy controls, MDD = major depressive disorder, N-R = nonremitted MDD, R = remitted MDD, ROI = region of interest.

the time series, and band-pass filtering (0.01–0.08 Hz) of the functional data was implemented to reduce the effects of low-frequency drifts and high-frequency physiological noise. Image preprocessing was conducted using the Data Processing Assistant and Resting-State fMRI (DPARSF) program.[51] Whole-brain volumes from the individual 3D structural images of all patients and HCs were processed using Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) on the MATLAB R2008a platform (The Mathworks, Natick, Massachusetts).

fALFF Analysis

Filtered time courses were first converted to frequency domain signals using the fast Fourier transform.[52] The ALFF

Figure 2. Two-Sample *t*-Test Analysis of Differences in Left Ventral ACC and Right Precuneus Among Recurrent and Remitted MDD Patients[a]



[a]Color bars represent *t* values from the 2-sample *t* test analysis of each pair (N-R vs HC, N-R vs R, and R vs HC) after controlling for age, sex, and educational level.
Abbreviations: ACC = anterior cingulate cortex, HC = healthy controls, N-R = nonremitted (recurrent) MDD, MDD = major depressive disorder, R = remitted MDD.

was then generated by calculating the averaged square root of the Fourier coefficient across 0.01–0.08 Hz for each voxel.[40,53] The fALFF is the fraction of ALFF in the low-frequency band (eg, 0.01–0.08 Hz) to the ALFF over the entire frequency range (eg, 0–0.25 Hz).[41,53] The standardized fALFF of each voxel was obtained by taking the ratio of its raw fALFF value to the global mean fALFF value within a brain mask to reduce the global effects of variability across participants.[40,54]

Statistical Analysis

A 1-way analysis of variance (ANOVA) was performed to examine voxel-by-voxel differences in the fALFF maps across the 3 groups with age, sex, educational level, and whole-brain volume included as covariates. Following the ANOVA, 2-sample *t* tests were implemented to determine the pairwise differences between recurrent MDD and remitted MDD, recurrent MDD and HC, and remitted MDD and HC, and pooled MDD and HC groups in a voxel-by-voxel manner with age, sex, and educational level included as covariates. Voxel-wise Pearson correlation coefficient analyses were performed to examine the relationship between various clinical measures (eg, the number of depressive episodes and the duration of illness) in the pooled patient group (ie, those with remitted and recurrent MDD) and the fALFF values with age, sex, and educational level included as covariates. An individual voxel threshold of $P < .01$ and a cluster size of 486 mm^3 (18 voxels) were used, which corresponds to a corrected $P < .05$ as determined by Monte Carlo simulations in the AFNI AlphaSim program (http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html) for all tests.

RESULTS

Demographic Information and Standardized Tests

As shown in Table 1, no significant differences in age, sex, or educational level were found among the 3 groups. HDRS and HARS scores were higher for patients in the recurrent MDD group than in the remitted MDD group.

fALFF Comparisons Among the 3 Groups

There was no significant difference in whole-brain volume among the 3 groups ($F = 0.220$, $P = .803$, Supplementary eFigure 1). One-way ANOVA revealed significant differences across the 3 groups ($P < .05$, corrected) in the left anterior cingulate cortex, right precuneus, left middle temporal gyrus, right amygdala, left postcentral gyrus, right cerebellum posterior lobe, and left superior temporal gyrus (Figure 1).

Compared to patients in the remitted MDD and HC groups, patients in the recurrent MDD group exhibited significantly increased fALFF values in the ventral ACC (subgenual cingulate) and decreased values in the right posterior insula and right precuneus (2-sample *t* test, $P < .01$, cluster size = 18; Figure 2 and Supplementary eFigure 2). In addition, patients in the recurrent MDD group exhibited

Table 2. fALFF Value Comparisons Between Patients With Recurrent MDD (Nonremitted, N-R), Patients With Remitted MDD (Remitted, R), and Healthy Controls (HC)

Brain Regions	Side	Brodmann Areas	Coordinates x	y	z	K	*t* Statistic
N-R > R							
Ventral ACC[a]	left	32	−3	−27	−9	24	3.52
Parahippocampus	left		−15	0	−30	23	3.67
Amygdala	right		21	0	−18	22	3.80
N-R > HC							
Ventral ACC[a]	left	32	−9	30	−6	99	5.06
Orbitofrontal gyrus	left	11	−39	42	−15	18	4.27
dmPFC	left	9, 10	−6	51	18	30	3.61
Middle temporal gyrus	right	21	57	−9	−21	34	3.92
N-R < R							
Posterior insula[a]	right		33	−33	18	18	4.10
Precuneus[a]	right		9	−81	39	23	3.59
Middle occipital lobe	right		42	−78	0	21	3.20
N-R < HC							
Posterior insula[a]	right		27	−30	18	20	3.85
Precuneus[a]	right		12	−81	39	21	4.11
Postcentral gyrus	left		−45	−21	57	42	4.11
Fusiform	left		−30	−63	−3	20	3.34
Inferior occipital lobe	left	37	−54	−72	−3	26	3.88
Middle occipital lobe	left	18	−15	−99	0	28	4.90
R > HC							
Middle frontal gyrus	left	10	−21	63	21	18	3.43
R < HC		…	…	…	…	…	…

[a]These regions were commonly found to exhibit both N-R > R and N-R > HC or both N-R < R and N-R < HC contrasts.
Abbreviations: ACC = anterior cingulate cortex, dmPFC = dorsomedial prefrontal cortex, fALFF = fractional amplitude of low-frequency fluctuation, K = cluster number, MDD = major depressive disorder.
Symbol: … = not applicable.

significantly different fALFF values in several regions compared to patients in the remitted MDD group (2-sample *t* test, $P < .01$, cluster size = 18); however, these regions were different from the regions that differed between the recurrent MDD and HC groups. Specifically, compared with the HC group, patients in the recurrent MDD group exhibited significantly increased fALFF values in the left orbitofrontal gyrus, left dorsomedial prefrontal cortex (dmPFC), and right middle temporal gyrus, and decreased fALFF values in the left inferior occipital lobe, left middle occipital lobe, left fusiform gyrus, and left postcentral gyrus (2-sample *t* test, $P < .01$, cluster size = 18). These differences were not found when comparing patients in the recurrent MDD group with patients in the remitted MDD group. Compared to patients in the remitted MDD group, patients in the recurrent MDD group exhibited significantly increased fALFF values in the left parahippocampus and right amygdala as well as decreased fALFF values in the right middle occipital lobe (2-sample *t* test, $P < .01$, cluster size = 18). The only difference between the remitted MDD group and the HC group was an increase in the fALFF value in the left middle frontal gyrus (Table 2). None of the brain regions in the remitted and recurrent MDD groups exhibited common fALFF value changes when compared with the HC group. Detailed information about the clusters across groups is presented in Table 2. Further, we ran a nonparametric Mann-Whitney *U* test that confirmed the 2-sample *t* test results. The Mann-Whitney *U* test results for the precuneus remained significant even after controlling for age, sex, educational level, and whole-brain volume in the recurrent MDD group compared to that from the remitted MDD group ($U = 107$, $P < .01$) and to the HC group ($U = 387$, $P < .01$). However, no significant difference was identified between the remitted group and the HC group ($U = 640$, $P = .311$).

Correlation Analyses in Pooled Patients With Recurrent MDD and Remitted MDD

Our voxel-wise regression analysis after pooling patients with recurrent MDD and remitted MDD revealed that fALFF values in the right precuneus (peak coordinate: 3, −45, 42; $R = -0.69$; $P < .01$) and right middle insula (peak coordinate: 39, 3, 6; $R = 0.60$; $P < .01$; Figure 3) were significantly correlated with number of depressive episodes. We also found that reduced fALFF values in the right precuneus (peak coordinate: 0, −66, 42; $R = -0.58$; $P < .01$; Figure 4) were significantly correlated with the duration of illness. Detailed correlation results between the fALFF measurements and the number of depressive episodes or illness duration in recurrent MDD and remitted MDD are presented in Table 3 and Supplementary eTable 1.

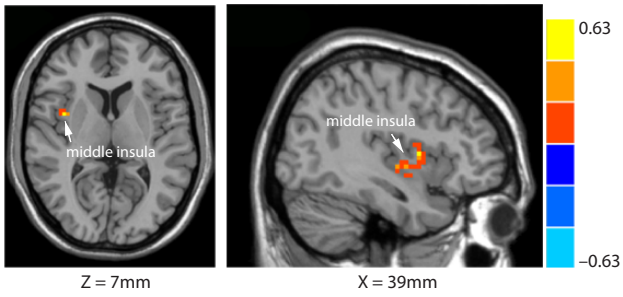
DISCUSSION

In this study, we compared resting-state fALFF values between HC subjects and patients experiencing recurrent depression. We expected to find a generally hyperactive DMN in patients with recurrent depression; instead, we found significantly decreased fALFF values in the precuneus and posterior insula in the recurrent MDD group compared with both the remitted MDD and HC groups. However, we did find significantly increased fALFF values in the anterior portion of the DMN, namely the left ventral ACC, and in the mPFC and lateral orbitofrontal cortex. Further, we observed reduced fALFF values in the fusiform and occipital areas in the recurrent MDD group compared with the HC group. Importantly, decreased precuneus activity ($R = -0.69$; $P < .01$ in pooled MDD patients; $R = -0.75$; $P < .01$ in recurrent MDD patients; $R = -0.63$; $P < .01$ in remitted MDD patients) and elevated middle insular activity ($R = 0.60$; $P < .01$ in pooled MDD patients; $R = 0.78$; $P < .01$ in recurrent MDD patients; $R = 0.41$; $P < .01$ in remitted MDD patients) during the resting state were found to be significantly correlated with depressive episodes, indicating a possible link among the precuneus, posterior insula, and "state" or "stage" of depression.

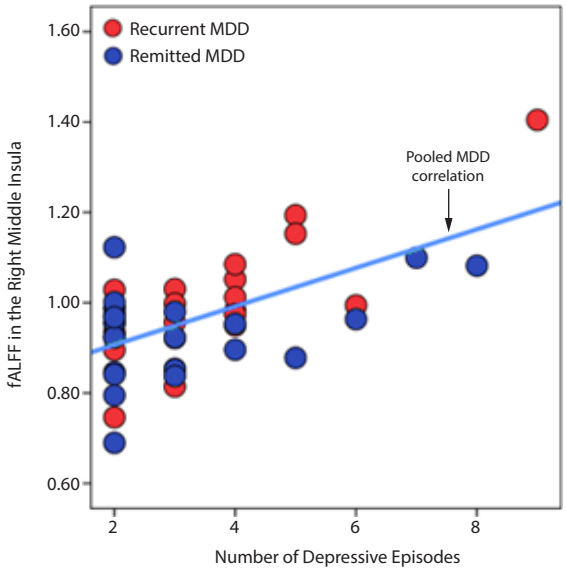
Reduced resting-state activity in the posterior DMN (eg, precuneus/dorsal PCC) of the recurrent MDD group appears inconsistent with previous findings, which generally report increased activity or connectivity in the DMN. However, our findings may not necessarily contradict previous results if the heterogeneity of the DMN is considered. For instance, activity in the dorsal PCC (which is adjacent to the precuneus) was positively correlated with activity in other regions in the DMN as

Figure 3. Correlation Between fALFF Values in Right Middle Insula and the Number of Depressive Episodes Among Pooled Patients With Recurrent and Remitted MDD

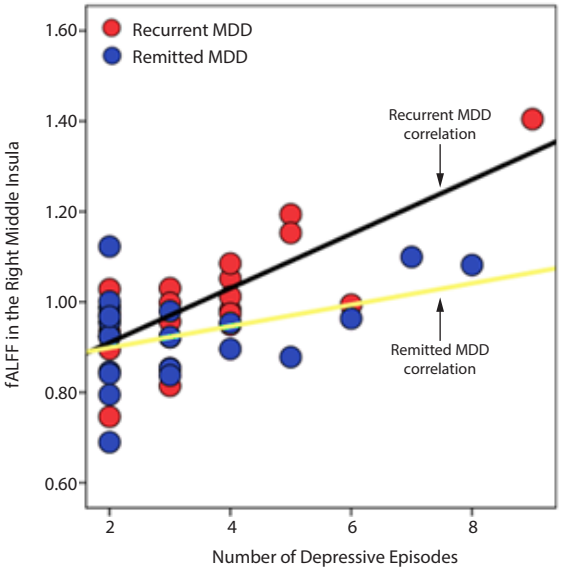
A. Brain Scan Showing Significant Positive Correlations Between Right Middle Insula and Number of Depressive Episodes[a]



B. Correlation Between fALFF in the Right Middle Insula and Number of Depressive Episodes in Pooled MDD Group (including recurrent MDD and remitted MDD)



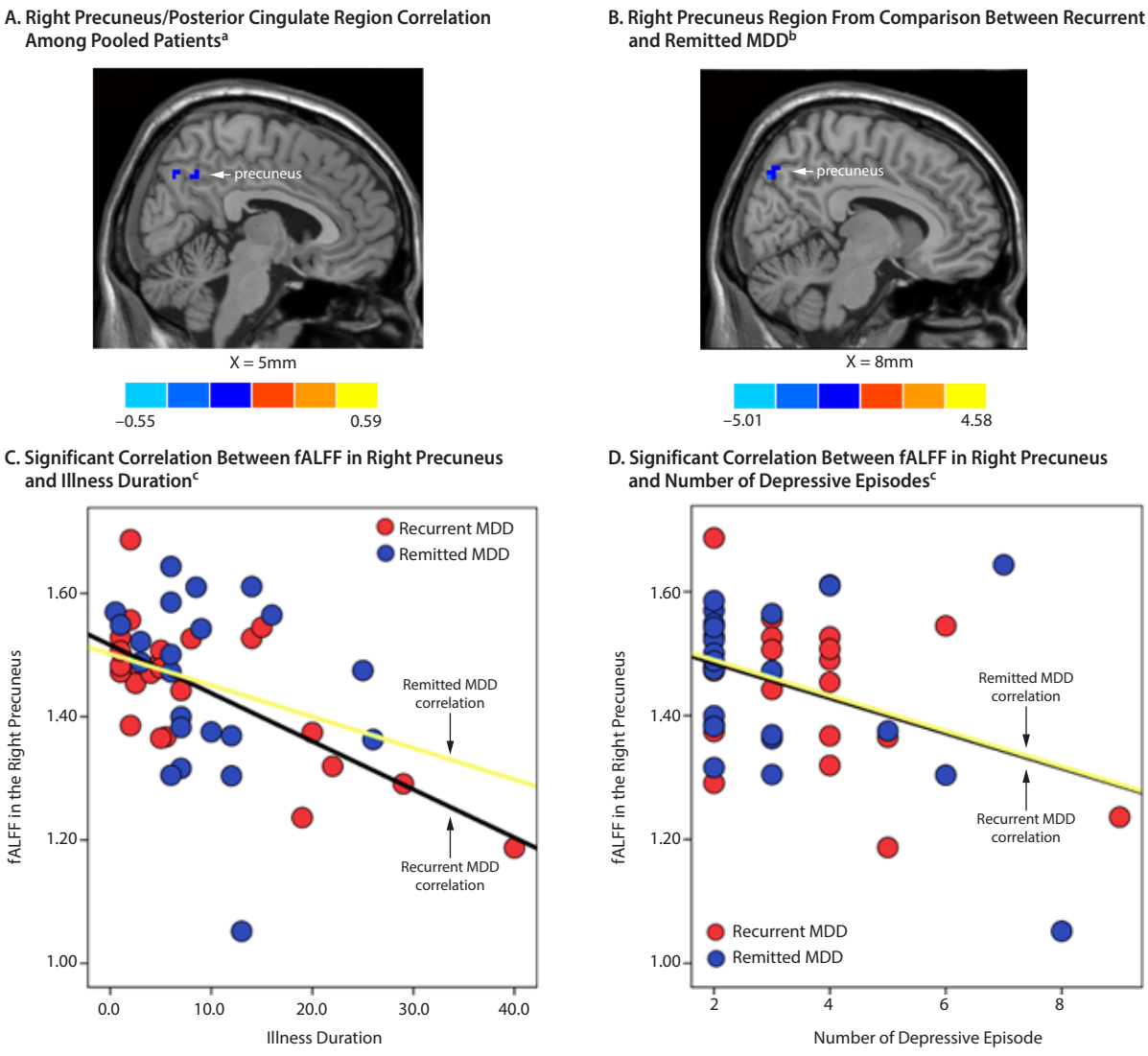
C. Correlation Between fALFF in the Right Middle Insula and Number of Depressive Episodes in Recurrent MDD Group and Remitted MDD Group, Respectively



[a]Voxel-wise analysis revealing a significant positive correlation between the fALFF value of the right middle insula (peak coordinate: 39, 3, 6) and the number of depressive episodes in pooled patients with recurrent MDD and remitted MDD. The color bar represents the correlation coefficient value.
[b]The left scatter plot confirms the correlation between fALFF in the right middle insula and the number of depressive episodes. The ROI was a sphere with 5-mm radius using peak coordinates from the whole-brain voxel-wise correlation analysis of the right middle insula as centers (blue line). Note that the insula region is different from the posterior insula regions, which exhibited reduced fALFF values in the recurrent MDD group compared to the remitted MDD and healthy control groups. The right scatter plot confirms the correlation between fALFF values in the right middle insula and the number of depressive episodes for both recurrent (black line) and remitted (yellow line) MDD.
Abbreviations: fALFF = fractional amplitude of low-frequency fluctuation, MDD = major depressive disorder, ROI = region of interest.

well as within regions in the attentional network at rest.[55, 56] It has been theorized that the dorsal PCC may therefore play a role in modulating the dynamic interaction between the DMN and the attentional control network for the efficient allocation of attention.[55] In addition, there are a number of studies indicating that the precuneus participates in attentional processing.[56,57] Therefore, we argue that reduced resting activity in the precuneus/dorsal PCC region observed in patients with recurrent depression may be a manifestation of reduced attentional control capacity during the resting state. Although we did not observe significantly decreased fALFF values in the precuneus of the remitted MDD group relative to the HC group, we did find a negative correlation between reduced fALFF in the precuneus and the progression of the disorder, ie, in terms of both the duration of illness and the number of depressive episodes. These results indicate that despite partial recovery of reduced resting activity in the precuneus/dorsal PCC, such reductions in resting activity may accumulate in the precuneus as the number of depressive episodes increases. We did find increased resting activity in the DMN in the recurrent MDD group relative to the HC group, but this activity was in the anterior portion of the DMN, including the left ventral ACC, dmPFC, and lateral orbitofrontal cortex. The ventral ACC has been identified in the spatial extent of the DMN in MDD. For instance, Greicius and colleagues[20] applied independent component analysis and found that activity in the thalamus and ventral ACC contributed more to DMN activity in

Figure 4. Correlation Between fALFF Values in Right Precuneus/Posterior Cingulate Region and Illness Duration/Number of Depressive Episodes Among Pooled Patients With Recurrent and Remitted MDD



[a]The fALFF values in the right precuneus/posterior cingulate region was significantly correlated with the number of depressive episodes in pooled patients with recurrent MDD and remitted MDD (peak coordinate: 0, −66, 42).
[b]The right precuneus region showed significantly reduced fALFF values in patients with recurrent MDD relative to those with remitted MDD when controlling for age, sex, educational level, and whole-brain volume. The 2 right precuneus clusters were close but did not overlap.
[c]Scatter plots confirm the correlation between fALFF in the right precuneus and illness duration (left) and number of depressive episodes (right) using an ROI analysis. The ROI was a sphere with 5-mm radius using peak coordinates from whole-brain voxel-wise correlation analysis as centers to ensure the correlations were not due to outliers for both recurrent (black line) and remitted (yellow line) MDD groups.
Abbreviations: fALFF = fractional amplitude of low-frequency fluctuation, MDD = major depressive disorder, ROI = region of interest.

patients with MDD than in the HC group. Hamilton et al[58] found mutually excitatory activation between the ventral ACC and mPFC using Granger causality analysis among components of the DMN in depression. Thus, the ventral ACC adjacent to the ventral mPFC is an important node within the DMN as well as in the corticolimbic circuits. Dysfunction in this region in patients with MDD has been well documented in the literature.[20,59–62] Previous studies have reported elevated functional connectivity between the subgenual ACC and insula,[63] amygdala,[59] and thalamus[20] in patients with MDD compared with HC subjects. The overactive ventral ACC during the resting state in recurrent depression may be related to exaggerated self-referential bias and failed emotional control in MDD, which is a core issue of chronic self-focus and negative rumination in recurrent depression.[64,65] As an extension of previous findings, we found increased ventral ACC and dmPFC activity in patients with recurrent MDD versus those with remitted MDD, which suggests that elevated anterior DMN activity may be related to the depressive state.

The disassociation pattern within the DMN as revealed by our study is of particular interest because it demonstrates a depression–state-related regionally varying pattern. Abnormal local activity in the dmPFC and precuneus almost

Table 3. Correlation Results Based on Voxel-Wise Correlation Analysis Between fALFF Measurements and Number of Depressive Episodes or Illness Duration in Both Recurrent MDD and Remitted MDD Patients

		Recurrent MDD		Remitted MDD	
Correlation With Brain Region	Side	*r*	*P*	*r*	*P*
Number of depressive episodes					
Positive correlation					
Ventral anterior insula	left	0.85	<.01	0.06	.80
Middle insula	right	0.78	<.01	0.41	.03
Dorsal anterior insula	left	0.71	<.01	0.37	.45
Supramarginal gyrus	right	0.69	<.01	0.59	<.01
Middle cingulate	right	0.58	<.01	0.65	<.01
Amygdala	left	0.75	<.01	0.30	.09
Negative correlation					
Precuneus	right	−0.75	<.01	−0.63	<.01
Superior parietal lobe	right	−0.69	<.01	−0.45	.04
Illness duration					
Negative correlation					
Precuneus	left	−0.76	<.01	−0.40	.03

Abbreviations: fALFF = fractional amplitude of low-frequency fluctuation, MDD = major depressive disorder.

identically mirrors the pattern of attentional modulation that was shown to affect subsequent emotional and neutral experiences in a longitudinal study on MDD.[66] Although impaired attentional gain modulation in the dmPFC was restricted to positive pictures during acute depressive episodes, general impairment in dmPFC activation in response to neutral pictures was identified during remission. In addition, van Tol et al[24] reported reduced cortical thickness in the dmPFC, middle frontal gyrus, and precuneus cortices in patients with depression. Those patients with thinner precuneus cortices had less significant functional connectivity between the dmPFC and precuneus in recurrent MDD, suggesting disconnectivity within regions of the DMN. Inverse alterations of fALFF values observed in the current study are therefore consistent with the reduced functional connectivity identified between the 2 regions in the van Tol study. The correlation between reduced dmPFC-precuneus functional connectivity and cortical thinness of the precuneus in patients with MDD suggests that the reverse relationship between the dmPFC and precuneus may be a consequence of long-term deficits in the precuneus. Pathological changes in the precuneus identified by a histologic study also support the long-term effects of depression in this region.[67] Structural changes in the precuneus were correlated with negative self-concepts in patients with major depression.[19] In agreement with these observations, our findings show that reduced resting-state activity in the precuneus but not the anterior portion of the DMN was correlated with the number of depressive episodes. Therefore, our results confirm the link between deficits in the precuneus and depression relapse.

In addition to the DMN findings, we found reduced fALFF values in the right posterior insula in the recurrent MDD group compared with the remitted MDD and HC groups. Similar to the DMN findings, decreased fALFF values in the right posterior insula also may be a state marker for depression.[22,68] Dysfunction of the insula in depression has been reported in a number of studies. For example, Liu et al[69] found decreased regional homogeneity in the right insula in both patients with MDD and their unaffected first relatives compared to HC subjects. Sprengelmeyer et al[70] proposed that bilateral insula gray matter volume in patients with MDD is negatively correlated with depression severity scores. Avery et al[71] also identified decreased activity in the bilateral insular cortex during an interoceptive attention task in unmedicated patients with MDD. In our previous study, we also found that patients with active MDD had decreased regional homogeneity in the right insula relative to patients with bipolar depression and to HC subjects during a resting state.[72] Converging evidence from task-related,[73] resting-state,[69] and structural[70] MRI studies suggests that decreased insular function may be a core deficit in depression and a feature of recurrent depression. Paradoxically, in the present study we found a positive correlation between stronger fALFF values (rather than decreased fALFF values) in the right mid/posterior insula and the number of depressive episodes. It is noteworthy that this insula region is more anterior to the region that showed decreased fALFF values in the recurrent MDD group compared with the other 2 groups. This discrepancy between the results from group comparisons and those from regression analysis may be because the anterior, mid, and posterior insula have different functions[74] and warrants further clarification in future studies. The correlation between fALFF values in the mid insula and the number of depressive episodes suggests that the right mid/posterior insula may be a region vulnerable to accumulated challenges from depressive episodes. Further studies are necessary to examine whether altered fALFF values in the insula can predict future depressive episodes.

Limitations

There are several limitations to our present study. First, almost all of the patients were on medication at the time of the scan due to serious practical and ethical issues, and consequently we cannot rule out possible confounding effects of medication. As we did not collect detailed lifetime data (eg, duration of medication and dose), we could not incorporate these data into the analyses as covariates. Second, an inability to control mind wandering in participants and an inability to collect physiological data (eg, depth of respiration, heart rate, ventricle size, and cerebrovascular network architecture) during the imaging procedure are disadvantages of resting-state fMRI studies. Future studies should be conducted to record cardiac and respiratory signals simultaneously with fMRI scanning to suppress effects induced by physiological-related noise in the cerebrospinal fluid and near large blood vessels. Third, there were no first-episode patients with MDD recruited for comparison, and our unbalanced sample sizes may have some influence on the results from between-group analysis. Fourth, tasks were not involved in the present study, but such tasks should be included in future studies to assess "switching" between resting and activation states. Despite these limitations, this study has a number of noteworthy strengths.

Strengths

First, we included not only patients with active recurrent depression but also those with remitted recurrent depression, which enabled us to understand depression–state- versus trait-related changes. Second, in contrast to previous opinions that only depression–trait-related changes are associated with future depressive episodes, we found that depression–state-related alterations during resting-state activity are associated with the number of depressive episodes. Third, decreased fALFF in the precuneus and increased fALFF in the right mid insula and amygdala became more marked as the number of depressive episodes increased.

Conclusions

We found altered resting-state activity in recurrent depression in nodes distributed throughout a wide range of neural networks, including the DMN (precuneus), salience network (insula), automatic emotion regulation network (ventral ACC, mPFC, and orbitofrontal cortex), and visual network (occipital lobe and fusiform gyrus). Although replication is warranted, disturbed functional changes in these networks, especially the inverse relationship between the anterior and posterior DMN, may serve as a psychopathological model for examining recurrent depression.

Submitted: April 4, 2015; accepted May 2, 2016.

Online first: March 14, 2017.

Drug names: carbamazepine (Tegretol, Epitol, and others), clonazepam (Klonopin and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), valproic acid (Depakene and others).

Potential conflicts of interest: The authors report no biomedical financial interests or potential conflicts of interest.

Funding/support:.

Dr Chun-Hong Liu received support from the National Natural Science Foundation of China grant 81471389 and from the High-Level Health Technical Personnel in Beijing grant 2014-3-095. Dr Zhen Yuan received support from University of Macau grants MYRG 2015-00036-FHS and MYRG2016-00110-FHS as well as Macau Science and Technology Development Fund grant 025/2015/A1 from the Macau government.

Role of the sponsor: The supporters had no role in the design, analysis, interpretation, or publication of this study.

Acknowledgments: The authors gratefully acknowledge the Beijing Normal University Imaging Center for Brain Research and Yu-Feng Zang, PhD, MD, from the Center for Cognition and Brain Disorders at Hangzhou Normal University for their contributions to our fMRI data acquisition. Dr Zang reports no biomedical financial interests or potential conflicts of interest.

Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Decreased Resting-State Activity in the Precuneus Is Associated With Depressive Episodes in Recurrent Depression

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DOI Number: https://doi.org/10.4088/JCP.15m10022

List of Supplementary Material for the article

1. **eFigure 1** Whole brain volume for recurrent major depressive disorder (MDD), remitted MDD, and healthy controls (HC)
2. **eFigure 2** Group comparison results based on 2-sample *t*-tests that controlled for age, sex, and educational level in patients with recurrent MDD (non-remitted, N-R) versus those with remitted MDD (remitted, R)
3. **eTable 1** Voxel-wise correlation analysis between the fALFF measurements and number of depressive episodes and illness duration in pooled patients with recurrent MDD and remitted MDD

Disclaimer

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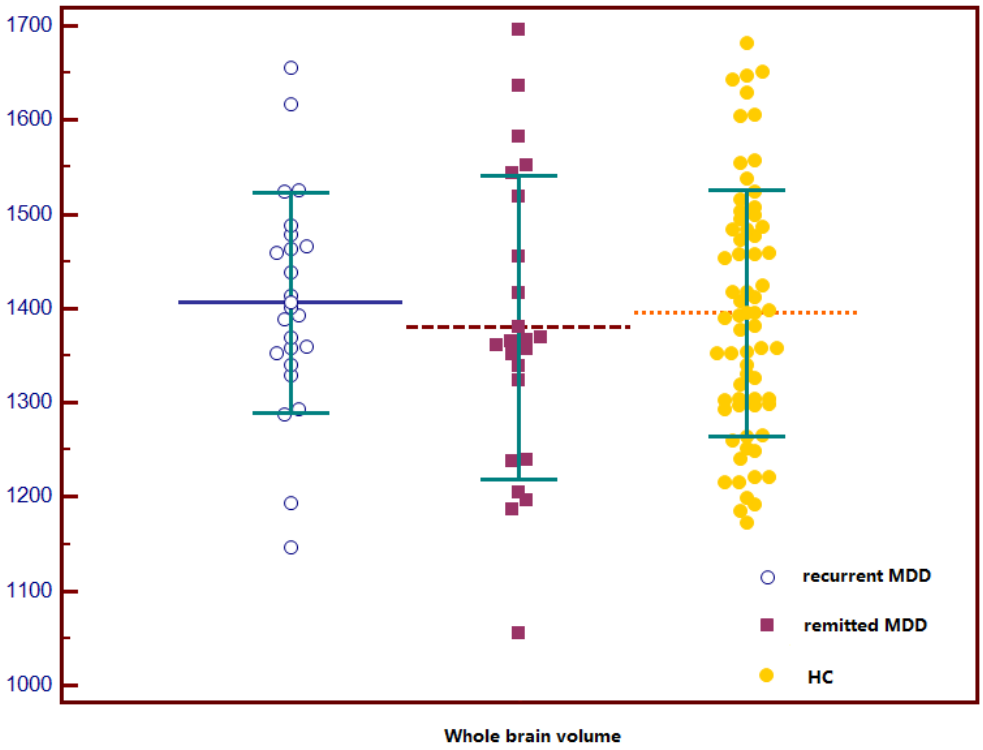
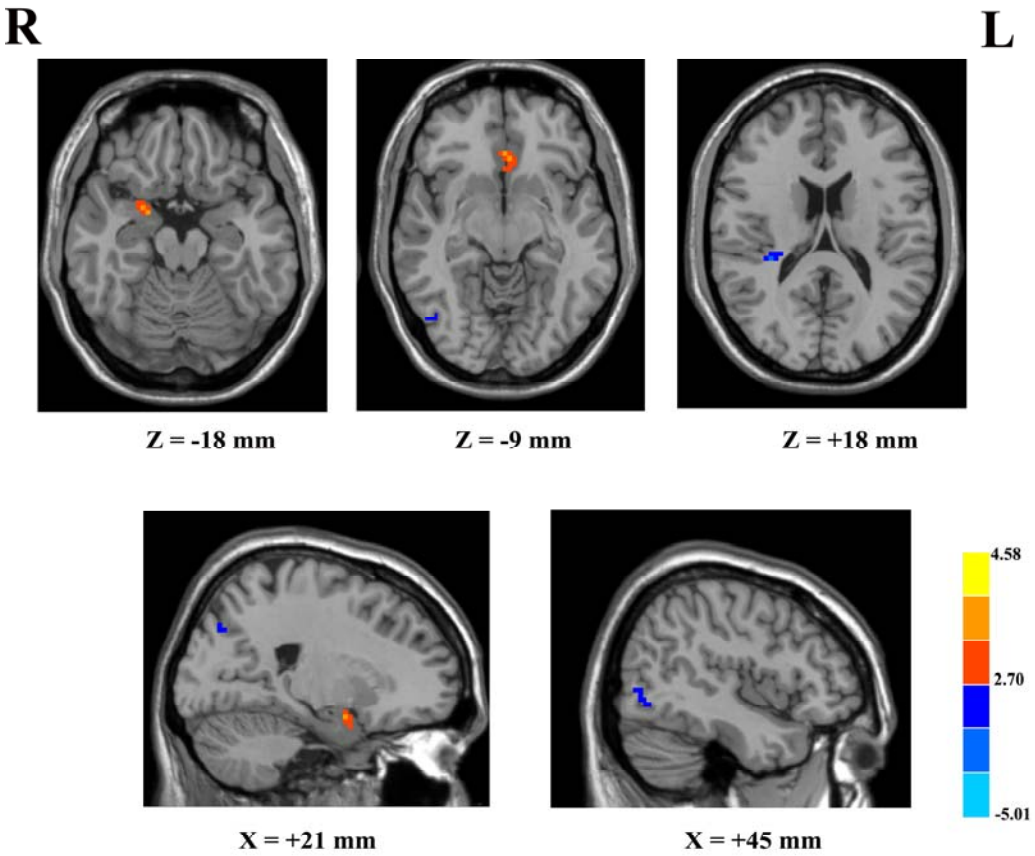
Supplementary eTable 1. Voxel-wise correlation analysis between the fALFF measurements and number of depressive episodes and illness duration in pooled patients with recurrent MDD and remitted MDD.

Correlation	Brain region	Side	Talairach coordinates x	y	z	Voxels	*r*	*p*
Number of depressive episodes	**Positive correlation**							
	Ventral AI	left	-39	0	-24	32	0.54	<0.01
	Middle insula	right	39	3	6	41	0.60	<0.01
	Dorsal AI	left	-36	21	-3	39	0.56	<0.01
	Supramarginal gyrus	right	45	-27	27	30	0.64	<0.01
	Middle cingulate	right	12	18	39	18	0.62	<0.01
	Amygdala	left	-21	0	-21	22	0.55	<0.01
	Negative correlation							
	Precuneus	right	3	-45	42	91	-0.69	<0.01
	Superior parietal lobe	right	24	-51	66	21	-0.56	<0.01
Illness duration	**Negative correlation**							
	Precuneus	left	0	-66	42	22	-0.58	<0.01

Abbreviations: MDD, major depressive disorder; fALFF, fractional amplitude of low-frequency fluctuation. AI: anterior insula.



Supplementary eFigure 1. Whole brain volume for recurrent major depressive disorder (MDD), remitted MDD, and healthy controls (HC).



Supplementary eFigure 2. Group comparison results based on two-sample *t*-tests that controlled for age, gender, and educational level in patients with recurrent MDD (non-remitted, N-R) versus those with remitted MDD (remitted, R).