# Identifying Functional Brain Abnormalities in Migraine and Depression Comorbidity

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# Abstract

**Background:** Migraine and major depressive disorder (MDD) are both high prevalence brain disorders and often comorbidity. However, the neural mechanisms underlying the migraine and depression comorbidity are largely unknown. We aimed to explore the brain functional abnormalities associated with the co-occurrence of migraine and depression.

**Methods:** High-resolution T1-weighted and resting-state functional magnetic resonance imaging were required from ninety-three well-matched subjects with migraineurs with depression, migraineurs without depression, patients with MDD and healthy controls (HC). Voxel-wise one-way and two-way analyses of variance in multiple functional variables were performed among the four groups. Furthermore, correlation analysis was conducted to detect the clinical significance of the altered brain functional regions.

**Results:** Migraineurs with depression showed functional alterations in the default mode network (DMN), pain processing network (PPN), and visual network (VN) compared with HC. Migraineurs without depression exhibited abnormalities in the DMN, PPN, VN, and ventral attention network compared with HC. Furthermore, the abnormalities in the right paracentral lobule and left calcarine were significantly correlated with emotional scales in the pooled migraine patients.

**Conclusions:** Migraineurs with and without depression revealed widely shared regional networks of function changes related to the DMN, PPN, and VN. Importantly, the right paracentral lobule and left calcarine may be the core regions for the neuropathological mechanism in migraine and depression comorbidity, and may contribute to the development of depression in migraineurs.


# Background

Migraine is a highly prevalent neurological disorder that affects more than 10% of adults around the world; women are three times more likely affected than men [1, 2]. It is typically characterized with a recurrent attack of headache, often accompanied by symptoms such as photophobia and phonophobia, nausea, vomiting, aura, premonitory symptoms, and a postdrome after headache subsides [3]. Depression or major depressive disorder (MDD) is a psychiatric disorder characterized by depressed mood, sleep abnormalities, cognition decline and vegetative symptoms; the lifetime prevalence of depression is approximately 20% [4]. The WHO predicted that depression will be the leading cause of disease burden by 2030 [5]. Numerous studies have consistently demonstrated that migraine and depression are often comorbid, which lead to more serious symptoms and poor treatment outcome [6, 7]. In addition, longitudinal studies have demonstrated that the multiple, bidirectional relationship between migraine and depressive disorder [6, 8]. The comorbidity predominantly may due to common underlying pathophysiologic and genetic mechanisms, involving abnormal brain development and brain activity, shared genetic basis, neurotransmitters and receptors, sex hormones as well as stress [8]. Therefore, due to the multifaceted interplay between migraine and depression, exploring the specific brain mechanisms

associated with migraine and depression comorbidity, may help refine precise clinical diagnosis, treatment, and research.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a non-invasive imaging technique to measure spontaneous brain activity based on the blood-oxygen-level-dependent (BOLD) signal [9, 10]. In the last decades, advances in rs-fMRI have made it great potential to evaluate the aberrations in the static functional activity of different brain regions and networks in patients with migraine and depression separately [11, 12]. A review including 28 articles reported interictal migraine compared with healthy controls had alterations of more than 20 functional connectivity (FC) networks [13]. Network based approach revealed the three most relevant networks related to migraineurs were the pain processing network (PPN), the default mode network (DMN), and the visual network (VN) [14–16]. In MDD patients, reproducibility of functional brain alterations with 1434 individuals reported that hypoactivity in the orbitofrontal, sensorimotor, and visual cortices and hyperactivity in the frontoparietal cortices compared to the controls [17]. A Meta-analysis of large-scale network dysfunction in MDD also revealed abnormal rsFC within and between brain networks involved in internally (DMN) or externally (dorsal attention network, DAN) oriented attention, processing of emotion (affective network, AN) or ventral attention Network (VAN), and goal-directed regulation of these functions (frontoparietal network, FN) [18]. Collectively, alterations in multiple functional areas have been reported in both migraine and MDD. However, few studies have explored the underlying functional mechanism with the comorbidity of migraine and depression.

In this study, we aimed to explore the potential brain function mechanism underlying the comorbidity of migraine and depression using rs-fMRI. Previous studies have demonstrated spontaneous neural activity can be reflected by the amplitude of low-frequency fluctuations (ALFF), fractional amplitude of low-frequency fluctuations (fALFF), and regional homogeneity (ReHo) in brain disorders [19, 20]. Therefore, first, we explored the group differences in ALFF, fALFF, and ReHo among the four groups by using a voxel-wise one-way analysis of variance (ANOVA). Second, we detected the main and interaction of migraine and depression by using voxel-wise two-way ANOVA with migraine and depression as between-subject factors on brain function. Finally, we explored the correlation between functional MRI abnormalities and subjects' performance, clinical and neuropsychological variables to evaluate their potential clinical significance.

## Methods

# Participants

A total of 93 subjects were enrolled in this study. Patients were recruited from the Neurologic Clinic of First affiliated hospital of Anhui Medical University and the Headache Clinic of First affiliated hospital of University of Science and Technology of China (USTC, Anhui Provincial Hospital), and the Hefei Fourth People's Hospital (Anhui Mental Health Center) between March 2019 and October 2020. This study was approved by the Research Ethics Committee of First affiliated hospital of Anhui Medical University, First

affiliated hospital of USTC, and Hefei Fourth People's Hospital. All subjects have written informed consent to participate in the study.

Migraine was diagnosed according to the third edition of the International Classification of Headache Disorders-3 (beta version) (ICHD-3 beta). The diagnosis of MDD was made according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria. The inclusion criteria of all subjects were 1) 18–55 years of age; 2) right handed; 3) Han ethnicity. The exclusion criteria were 1) a history of secondary or other concomitant primary headache disorders, significant neurological and physical diseases; 2) the presence of other psychiatric disorders such as schizophrenia, bipolar disorder, substance-induced mood disorder, anxiety disorders, substance abuse or dependence; 3) a history of head injury with loss of consciousness; 4) pregnancy or any contraindications for MRI. All patients were evaluated by at least two well-trained neurologists or two psychiatrists. All migraine patients were migraine-free for at least 3 days at the time of the MRI scan to avoid any possible interference from headache pain on the imaging results.

# Behavior Assessment and Subgroup Division

Demographic information (including age, gender, years of education) of the subjects were recorded. The migraine family history, migraine duration, Headache Impact Test-6 (HIT-6), Visual Analogue Scale (VAS), and Migraine Disability Assessment (MIDAS) were assessed for the impact of migraine [21–23]. The 17-item Hamilton Rating Scale for Depression (HAMD) [24], 14-item Hamilton Rating Scale for Anxiety (HAMA) [25], and Beck Depression Inventory-second edition (BDI-II) [26] score were applied for assessing the depression and anxiety status. Cognitive function was assessed with Mini-Mental State Examination (MMSE).

The subjects were divided into four subgroups, migraineurs with depression (M+/D+, n = 23), migraineurs without depression (M+/D-, n = 25), patients with major depressive disorder (M-/D+, n = 22), and healthy controls (M-/D-, n = 23).

# The M+/D + group

The subjects were diagnosed with migraine without aura and comorbid depression. They were all initially diagnosed with migraine and depression, and had not taken any regular medications for the treatment of migraine and depression during observation period. The 17-HAMD score of this group was greater than 7.

# The M+/D- group

The subjects were diagnosed with migraine without aura and had no history of any psychiatric disorders including MDD or depressive mood. They were all initially diagnosed migraine, and had not used any drugs to prevent migraine. The 17-HAMD score of this group was less than 7.

# The M-/D + group

The subjects were diagnosed with MDD. They had no history of migraine, other types of headache. All patients were receiving their regular antidepressant medications. The 17-HAMD score of this group was

greater than 7.

# The M-/D- group

The subjects were recruited through consented friends, university students and hospital workers. The M-/D- group comprised volunteers without migraine or depression. They had no family history of migraine and psychiatric disorders, and had not using medications. The 17-HAMD score of this group was less than 7.

# Image Acquisition

MRI scans were obtained using a 3.0-Tesla MR system (Discovery GE750w;GE Healthcare,Buckinghamshire, United Kingdom) with a 24-channel head coil at the Information Science Center of USTC. High-resolution 3D T1-weighted structural images were acquired using a brain volume (BRAVO) sequence with the following parameters: repetition time (TR) = 8.16 ms; echo time (TE) = 3.18 ms; flip angle (FA) = 12°; field of view (FOV) = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm, no gap; 188 sagittal slices. Resting-state BOLD data were acquired using a gradient-echo single-shot echo planar imaging (GRE-SS-EPI) sequence with the following parameters: TR = 2400 ms; TE = 30 ms; FA = 90°; FOV = 192 mm × 192 mm; matrix = 64 × 64; slice thickness = 3 mm, slice gap = 1 mm; 217 volumes. All participants were instructed to keep their eyes closed, relax, move as little as possible, and think of nothing in particular during scanning. None of the participants were excluded for visually inspected imaging artifacts.

# fMRI Data Preprocessing

The functional and anatomical data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM12, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing and Analysis for Brain Imaging (DPABI_V3.1_180801, http://rfmri.org/dpabi) in MATLAB (R2011a) [27]. The first 10 volumes for each participant were discarded to allow the signal to reach equilibrium and the subjects to adapt to the scanning noise. The remaining images were corrected by slicing time and realigned. All subjects' BOLD data were within the defined motion thresholds (i.e., translational or rotational motion parameters not exceeding 2.5 mm or 2.5◦). Several nuisance covariates (the linear drift, the estimated motion parameters based on the Friston-24 model, the spike volumes with frame-wise displacement (FD) > 0.5, the white matter signal, and the cerebrospinal fluid signal) were regressed out from the data. The data was then detrended, bandpass filtered from 0.01 to 0.1 Hz. In the normalization step, individual structural images were firstly co-registered with the mean functional image; then the transformed structural images were segmented and normalized to the MNI space using the DARTEL technique. Finally, each functional volume was spatially normalized to MNI space using the deformation parameters estimated during the above step and resampled into a 3-mm cubic voxel. After spatial normalization, all data sets were smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel.

# ALFF, fALFF, and ReHo calculation

ALFF was computed as the mean power spectrum in a specific low-frequency band (0.01–0.1 Hz) [28], and fALFF was the ratio of the power spectrum in the low-frequency band (0.01–0.1 Hz) to that in the entire frequency range [29]. ReHo was calculated as the Kendall's coefficient of concordance (or Kendall's W) of the time course of a given voxel with those of its nearest neighbours (26 voxels) [30]. ALFF, fALFF, and ReHo were calculated using DPABI software. For standardization purposes, the ALFF, fALFF, and ReHo of each voxel were divided by the global mean value within the whole-brain mask. Finally, the resulting ReHo images were spatially smoothed with a 6-mm FWHM Gaussian kernel.

# Statistical Analysis

# Demographic and Clinical Data

One-way ANOVA, two-samples *T*-tests and chi-square tests were conducted using the Statistical Package for the Social Sciences version 23.0 software package (SPSS, Chicago, ) to compare the continuous and categorical variables among groups. The significance was set at $P < 0.05$.

# fMRI Imaging

Voxel-wise one-way ANOVA was tested to explore group differences in ALFF, fALFF, and ReHo among the four groups using SPM 12. Voxel two-way ANOVA with migraine and depression as between-subject factors was performed on brain function to identify main and interaction effects of migraine and depression by using SPM 12. Comparisons above were corrected using a cluster-level family-wise error (FWE) method, resulting in a cluster defining threshold of $P = 0.001$ and a corrected cluster significance of $P < 0.05$. Then, the brain regions identified in the one-way and two-way ANOVA analyses were extracted as region of interest (ROIs). Post hoc tests were then performed on the ROIs using Bonferroni correction ($P < 0.05/4 = 0.0125$).

# The Relationship Between Functional Imaging Features and clinical variables

To further detect whether the intrinsic brain activity of the above ROIs were correlated with the clinical variables (Duration of illness, HIT-6, VAS, MIDAS, HAMD, HAMA, and BDI-II) in pooled migraine patients (including both the M+/D- and M+/D + groups) and MDD patients (including both the M-/D + and M+/D + groups), Pearson or Spearman coefficients correlation analyses were conducted. For these correlation analyses, a significant threshold was set at $P < 0.05$.

## Results

# Demographic and Clinical Characteristics

Demographic and clinical data of all the subjects are listed in Table 1. In this study, four groups were matched for age, sex, education level, and FD ($P > 0.05$). Significant differences for scores of HAMD, HAMA were observed among four groups ($P < 0.001$). Higher scores of HAMD, HAMA were recorded in the

groups of M+/D + and M-/D + than in the groups of M+/D- and M-/D- ($P < 0.001$). Higher scores of BDI-II were recorded in the M+/D + group than in the M+/D- group ($P < 0.001$). There were no significant differences for the scores of VAS, MIDAS, and HIT-6 in the M+/D- group compared with the M+/D + group ($P > 0.05$).

Table 1
Demographic and clinical characteristics for all subjects (n = 93).

| Characteristic | M+/D- (n = 25) | M-/D+ (n = 22) | M+/D+ (n = 23) | M-/D- (n = 23) | F/T/$\chi^2$ | *P* |
|---|---|---|---|---|---|---|
| Age (yeas) | 31.36 ± 7.47 | 35.55 ± 11.25 | 30.26 ± 6.52 | 32.74 ± 11.05 | 1.373 | 0.256 |
| Gender (female/male) | 18/7 | 18/4 | 19/4 | 19/4 | 1.211 | 0.750[a] |
| Family history of migraine | 17/25 | N/A | 16/23 | N/A | N/A | N/A |
| Duration of illness (days) | 104.40 ± 61.82 | 54.12 ± 84.09 | 101.22 ± 64.58 | N/A | 3.622 | 0.032 |
| Education (years) | 13.92 ± 3.41 | 11.32 ± 4.89 | 12.78 ± 4.62 | 14.09 ± 4.38 | 1.974 | 0.124 |
| FD (mm) | 0.09 ± 0.05 | 0.07 ± 0.03 | 0.10 ± 0.05 | 0.08 ± 0.02 | 2.620 | 0.056 |
| VAS | 6.16 ± 1.40 | N/A | 6.22 ± 1.20 | N/A | -0.151 | 0.880[b] |
| MIDAS | 16.76 ± 10.93 | N/A | 25.78 ± 22.73 | N/A | -1.775 | 0.082[b] |
| HIT-6 | 59.68 ± 5.14 | N/A | 60.91 ± 4.74 | N/A | -0.861 | 0.394[b] |
| HAMD | 3.76 ± 1.92 | 26.91 ± 3.93 | 17.35 ± 3.72 | 1.48 ± 1.90 | 364.318 | 0.000 |
| HAMA | 3.72 ± 2.65 | 23.23 ± 7.33 | 10.04 ± 4.77 | 1.57 ± 1.80 | 102.100 | 0.000 |
| BDI-II | 5.60 ± 3.37 | N/A | 22.39 ± 5.24 | N/A | -13.322 | 0.000[b] |

The data are shown as the mean ± SD. Abbreviations: M+/D+, migraineurs with depression; M+/D-, migraineurs without depression; M-/D+, patients with major depressive disorder; M-/D-, healthy controls; FD, frame-wise displacement; VAS, Visual Analogue Scale; MIDAS, Migraine Disability Assessment; HIT-6, Headache Impact Test; HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; BDI-II, Beck Depression inventory-II.

[a] The *P*- value was obtained by chi-square test;

[b] the *P*-value was obtained by two-sample *T* test;

other *P*-values was obtained by one way analysis of variance (ANOVA).

# Differences in ALFF Values Across Groups

A voxel-wise ANOVA revealed that the intergroup differences in ALFF were mainly located in the right precentral, the right paracentral lobule, the right inferior occipital gyrus (IOG), the right lingual, the right calcarine, and the left thalamus ($P < 0.05$, Cluster-level FWE-corrected) (Fig. 1; Table 2). The post hoc analyses revealed that the M+/D + patients exhibited significantly increased ALFF in the right precentral, the right paracentral lobule, the right IOG, the right lingual, and the right calcarine compared to that in the M-/D- subjects and in the paracentral lobule compared with that in the M+/D- subjects ($P < 0.05$, Bonferroni corrected). Meanwhile, the M+/D- subjects exhibited significantly increased ALFF in the right precentral, the right IOG, the right lingual, the right calcarine, and the left thalamus compared with that of the M-/D- ($P < 0.05$, Bonferroni corrected) (Fig. 1). In contrast, the significant main and interaction effect of migraine and depression on ALFF was not found.

Table 2
Brain areas with significant differences in the ALFF values among four groups.

| Clusters | Peak MNI Coordinates (x, y, and z) | Number of Voxels | Max *F* value |
|---|---|---|---|
| R Inferior occipital gyrus | 51, -72, -15 | 31 | 9.7992 |
| R Lingual | 21, -66, -3 | 141 | 10.7856 |
| R Calcarine | 6, -87, 0 | 39 | 8.1106 |
| R Precentral | 39, -9, 57 | 51 | 10.9265 |
| R Paracentral lobule | 3, -39, 72 | 68 | 15.5144 |
| L Thalamus | 0, -24, 12 | 32 | 9.5223 |

Abbreviations: ALFF, amplitude of low-frequency fluctuations; MNI, Montreal Neurological Institute; L, left; R, right.

# Differences in fALFF Values Across Groups

A voxel-wise ANOVA revealed that the intergroup differences in fALFF were mainly located in the left medial prefrontal cortex (mPFC, including the superior frontal gyrus, medial and superior frontal gyrus) ($P < 0.05$, Cluster-level FWE-corrected) (Fig. 2; Table 3). The post hoc analyses revealed that the M+/D + and M+/D- subjects exhibited significantly decreased fALFF in the left mPFC compared with that of the M-/D- subjects ($P < 0.05$, Bonferroni corrected) (Fig. 1). In contrast, the significant main and interaction effect of migraine and depression on fALFF was not found.

Table 3
Brain areas with significant differences in the fALFF values among four groups.

| Clusters | Peak MNI Coordinates (x, y, and z) | Number of Voxels | Max *F* value |
|---|---|---|---|
| L Superior frontal gyrus, medial | 6, 57, 9 | 61 | 9.4713 |
| L Superior frontal gyrus, dorsolateral | -21, 60, 21 | 32 | 8.6521 |

Abbreviations: fALFF, fractional amplitude of low-frequency fluctuations; MNI, Montreal Neurological Institute; L, left.

# Differences in ReHo Values Across Groups

Four regions, namely, the left IOG, the left calcarine, the left mPFC, and the right lingual showed significant ReHo differences among the four groups ($P < 0.05$, Cluster-level FWE-corrected) (Fig. 3; Table 4). The post hoc analyses revealed that the M+/D + subjects exhibited significantly increased ReHo in the left IOG and the left calcarine, while decreased ReHo in the left mPFC compared with that in the M-/D- ($P < 0.05$, Bonferroni corrected). Moreover, the M+/D- subjects exhibited significantly increased ReHo in the left IOG, the left calcarine, and the right lingual, while decreased ReHo in the left mPFC compared with that of the M-/D- ($P < 0.05$, Bonferroni corrected) (Fig. 3). In contrast, the significant main and interaction effect of migraine and depression on ReHo was not found.

Table 4
Brain areas with significant differences in the ReHo values among four groups.

| Clusters | Peak MNI Coordinates (x, y, and z) | Number of Voxels | Max *F* value |
|---|---|---|---|
| L Inferior occipital gyrus | -39, -69, -9 | 72 | 10.3109 |
| L Superior frontal gyrus, medial | 3, 66, 12 | 85 | 11.4504 |
| L Calcarine | -6, -75, 15 | 52 | 7.8709 |
| R Lingual | 36, -51, -9 | 121 | 12.5957 |

Abbreviations: ReHo, regional homogeneity; MNI, Montreal Neurological Institute; L, left; R, right.

# Main and Interaction Effects of Migraine and Depression on Brain Function

As illustrated in Fig. 4 and Table 5, a main effect of migraine on preprocessed function images was seen in the left inferior frontal gyrus (IFG), triangular part ($P < 0.05$, Cluster-level FWE-corrected). Moreover, a significant interaction effect of migraine and depression on the left calcarine gyrus was detected ($P < 0.05$, Cluster-level FWE-corrected). In contrast, a significant main effect of depression on brain function was not found.

Table 5
The main and interaction effects of migraine and major depressive disorder on brain function.

| Clusters | Peak MNI Coordinates (x, y, and z) | Number of Voxels | Max *F* value |
|---|---|---|---|
| Main effect of migraine | | | |
| L Inferior frontal gyrus, triangular part | -48, 36, 21 | 55 | 16.7927 |
| Interactive effect of migraine and major depressive disorder | | | |
| L Calcarine | -3, -99, 0 | 257 | 22.2694 |
| Abbreviations: MNI, Montreal Neurological Institute; L, left. | | | |

# Correlation Analyses

In the pooled migraine patients, the ALFF value in the right paracentral lobule was significantly positively correlated with the scores of HAMD (*rho* = 0.306, *P* = 0.035) and BDI-II (*rho* = 0.323, *P* = 0.025) in the pooled migraine patients (Fig. 5A; 5B), while the interaction effect of left calcarine gyrus was significantly negatively correlated with the HAMD (*rho* = -0.311, *P* = 0.032), HAMA (*rho* = -0.332, *P* = 0.021), and BDI-II scores (*rho* = -0.286, *P* = 0.048) (Fig. 5C; 5D; 5E).

In the pooled MDD patients, the ALFF, fALFF, and ReHo for all above ROIs were significantly correlated with the HAMD scores ($P < 0.05$). The ALFF, fALFF, and ReHo were significantly correlated with the HAMA scores for all above ROIs ($P < 0.05$) except the ALFF of left thalamus.

# Discussion

In the present study, we aimed to explore the brain function alterations specific to the comorbidity of migraine and depression using rs-fMRI in both migraine and MDD patients. Fourth major findings were reported. First, migraineurs with depression showed several areas with function alterations in the right precentral, right paracentral lobule, bilateral IOG, right lingual, bilateral calcarine, and left mPFC compared with HC. Second, intrinsic brain activity specific to migraine were mainly located in the right precentral, left thalamus, bilateral IOG, right lingual, bilateral calcarine, and left mPFC compared with HC. Third, a main effect of migraine was seen in the left IFG, triangular part; a interaction effect of migraine and depression was detected in the left calcarine. Fourth, the activity in the right paracentral lobule and left calcarine were significantly correlated with clinical variables (HAMD, HAMA, and BDI-II) in pooled migraine patients.

Migraineurs with comorbid depression showed significantly increased activity in the right precentral, the right paracentral lobule, the bilateral IOG, the right lingual, the bilateral calcarine; decreased activity in the left mPFC compared with the M-/D- subjects. Moreover, the interaction of migraine and depression was observed in the left calcarine. As the anterior node of the Default mode network (DMN), the mPFC was highly active at rest but inhibit activity mainly engaged in internally directed cognitions such as emotional

processing and self-referential activity [31, 32]. A previous study investigated that migraine and depression jointly affected the development of the left mPFC, which may contribute to determining the common symptoms in migraine and depression [33]. The precentral gyrus and paracentral lobule, thought to be part of Sensorimotor network (SMN) or PPN, related to detection and processing of sensory input (including pain) and preparation and execution of motor functions [34, 35]. The lingual, calcarine, and IOG were known as brain areas of VN, that was related visual perceptual processing and emotion [35]. Mengmeng Ma, et al also demonstrated migraineurs with comorbid depression had different developmental trajectories in the right fusiform and thalamus, which were associated with transmitting, controlling and remembering pain and emotion [33]. Taken together, the results presented here suggested that abnormalities in the DMN, PPN, and VN were profoundly involved in the neuropathological mechanism of co-occurrence of migraine and depression.

In this study, compared with HC, migraineurs without depression exhibited significantly increased activity in the right precentral, the bilateral IOG, the right lingual, the bilateral calcarine, the left thalamus; decreased activity in the left mPFC. Furthermore, the main effect of migraine was seen in the left IFG, triangular part. The IFG is part of the VAN, was suggested to be related to the stimulus-driven control attention [36]. The thalamus, a region of PPN, is considered to play an important role in the transmission of nociceptive inputs to cortical pain related brain regions, including lateral pathway (somatic sensory area) and medial pathway (the PFC and limbic system) [37, 38]. Converging evidence suggested patients with migraine have multiple brain regions and networks alterations, and more than 20 FC were reported, which overlapped mostly with our results [13, 39]. Thus, the aberrant activity in the DMN, PPN, VN, and VAN may further suggest the impairment of sensory processing, visual perceptual processing and emotion, cognitive (attention, self-related) were associated with migraine patients.

When combing the findings for the comparing M+/D + group and M+/D- group with healthy controls, abnormalities in the right paracentral lobule were observed in the migraineurs with depression, but not in the migraineurs without depression. Interestingly, analysis of ROI demonstrated that the ALFF value in the paracentral lobule was positively correlated with the scores of HAMD and BDI-II, while the interaction effect of left calcarine gyrus was negatively correlated with the HAMD, HAMA, and BDI-II scores in the pooled migraine patients. The paracentral lobule and calcarine are the initial stage of brain information reception and processing from the periphery, has been linked to the further advanced emotion processing and response [40, 41]. HAMD, BDI-II, and HAMA reflected overall severity of depression and anxiety symptoms in our patients. This result highlighted the role of the right paracentral and left calcarine, which were associated with depression and anxiety symptoms in the migraineurs and even result in comorbidity.

There are several limitations that should be highlighted in this study. First, the sample size is relatively modest, which may limit the statistical power in detecting subtle brain alterations, such as the group difference between M-/D + group and HC group and the main effect of MDD. Second, we cannot absolutely rule out the influence of antidepressant medication and illness duration on our results, due to practical and ethical issues. Future studies are intended to test the reproducibility of our findings by using

a larger sample of first-episode, medication-naïve patients. Finally, our cross-sectional design does not allow inference on causality. In the future, prospective longitudinal studies should be conduct whether these regional network alterations are a part of the pathogenesis or consequences of the comorbidity disorders.

# Conclusions

In the current study, we identified regional network functional alterations in patients with migraine and comorbidity migraine and depression. Migraineurs with and without depression revealed widely shared regional networks of function changes related to the DMN, PPN, and VN. Furthermore, our results indicated that the right paracentral lobule and left calcarine may be the core region for the mechanism in migraineurs with depression, which may responsible for the development of depression in migraineurs.

# Abbreviations

ALFF, amplitude of low-frequency fluctuations; BDI-II, Beck Depression Inventory-second edition; BOLD, blood-oxygen-level-dependent; DMN, default mode network; DPABI, Data Processing and Analysis for Brain Imaging; FC, functional connectivity; fALFF, fractional amplitude of low-frequency fluctuations; FWHM, full-width at half-maximum; FWE, family-wise error; HIT-6, Headache Impact Test-6; HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; IOG, inferior occipital gyrus; IFG, inferior frontal gyrus; MDD, major depressive disorder; MIDAS, Migraine Disability Assessment; mPFC, medial prefrontal cortex; PPN, pain processing network; ROI, region of interest; ReHo, regional homogeneity; rs-fMRI, resting-state functional magnetic resonance imaging; SMN, sensorimotor network, VN, visual network; VAN, ventral attention network; VAS, Visual Analogue Scale.

# Declarations

### Ethics approval and consent to participate

The Ethics Committee of First affiliated hospital of Anhui Medical University, First affiliated hospital of USTC, and Hefei Fourth People's Hospital approved the study and participants were asked to give their written informed consent to participate in the study.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analysed during this study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare no conflict of interest.


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### Authors' contributions

Xin Chen, Ying Liu and Ying Yang conceptualized and designed the study. Ying Yang was responsible for conducting the analyses, preparing the first draft of the manuscript, and preparing the manuscript for submission. Xin chen and Ying Liu was responsible for obtaining funding for the study, supervising the analyses, and editing drafts of the manuscript. Hongchun Zhang, Hongyun Hu, Li Yan, and Wei Gui were responsible for data collection and initial data preprocessing. All authors contributed to and approved the final manuscript.


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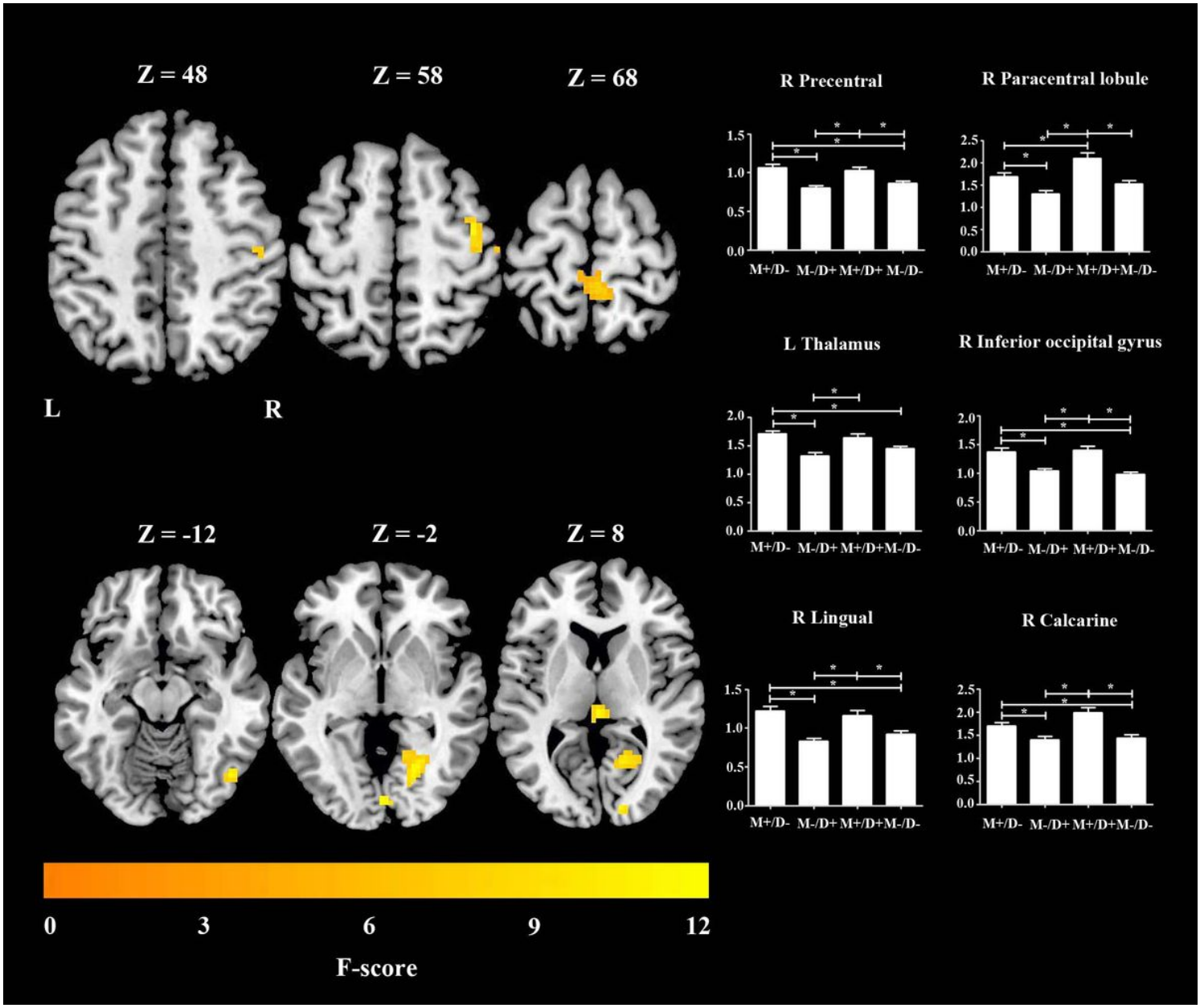
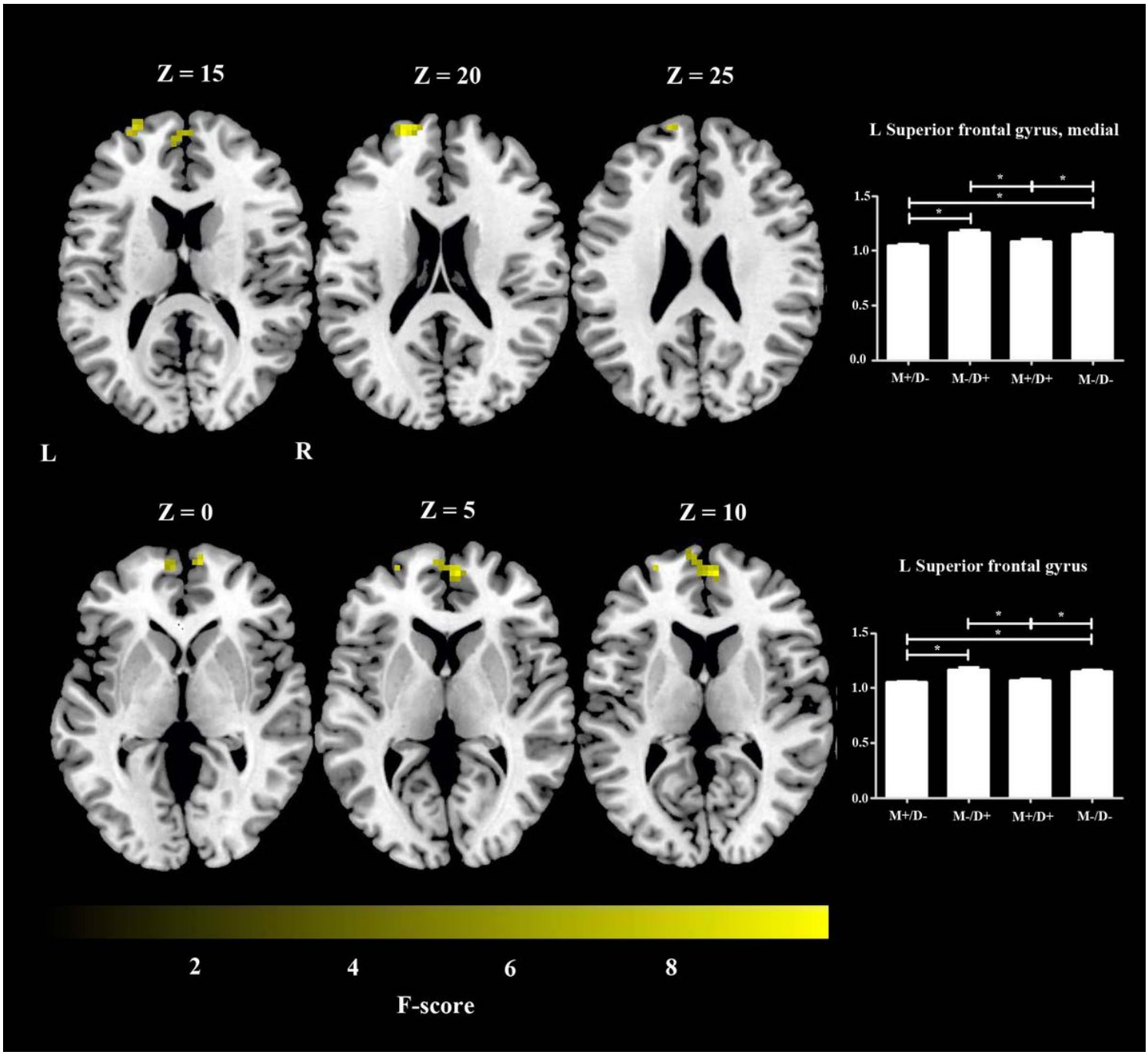
# Figures



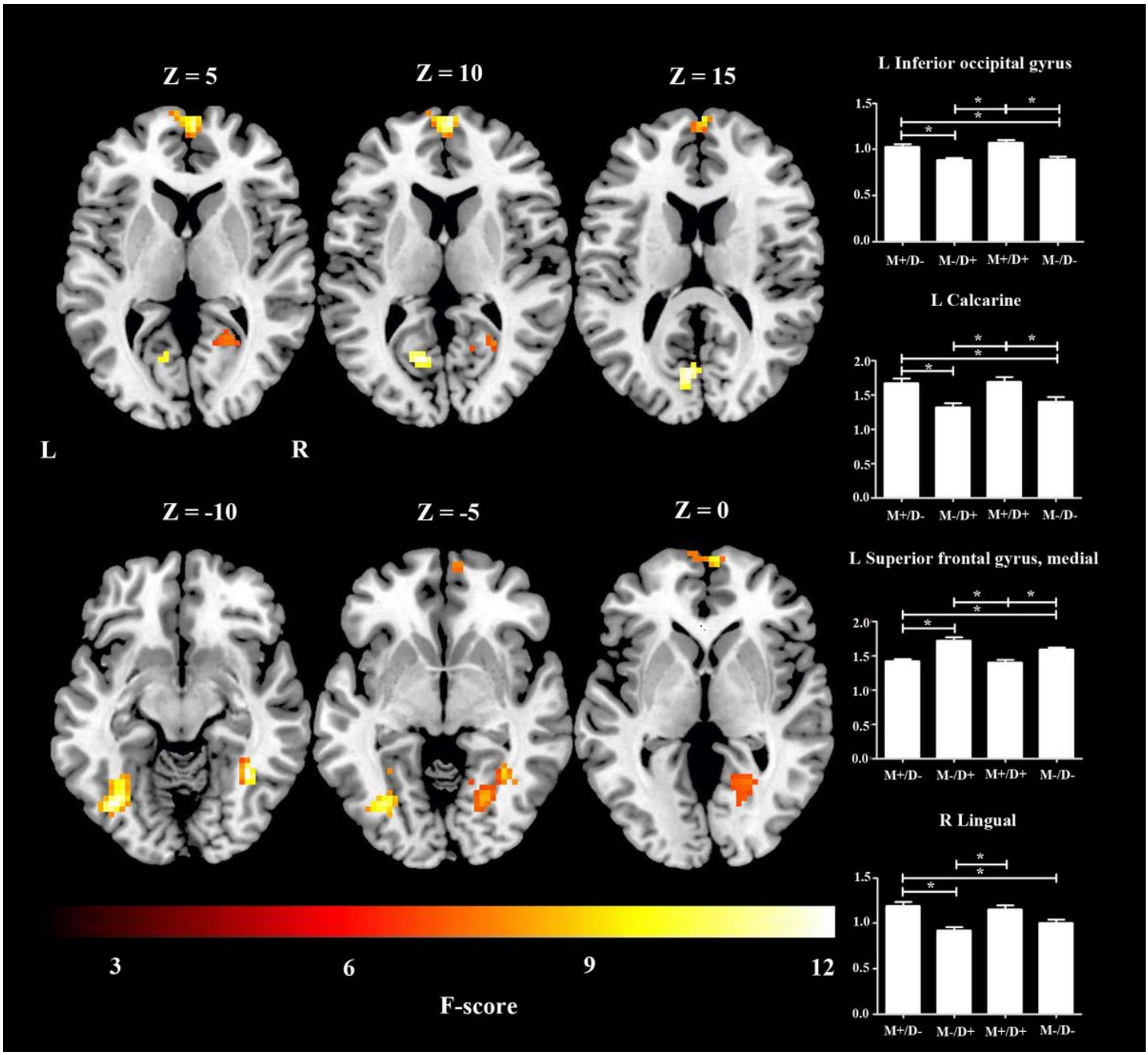

## Figure 1

One-way ANOVA analysis on ALFF among the four groups. Significant group differences in the right precentral, the right paracentral lobule, the right inferior occipital gyrus, the right lingual, the right calcarine, and the left thalamus. On the right, the histograms exhibited the mean ALFF value by group (error bars represents standard error from mean) in each identified ROI. Abbreviations: ALFF, amplitude of low-frequency fluctuations; ROI, region of interest; M+/D+, migraineurs with depression; M+/D-, migraineurs without depression; M-/D+, patients with major depressive disorder; M-/D-, healthy controls; L, left; R, right. * P < 0.05 (Bonfornni corrected).



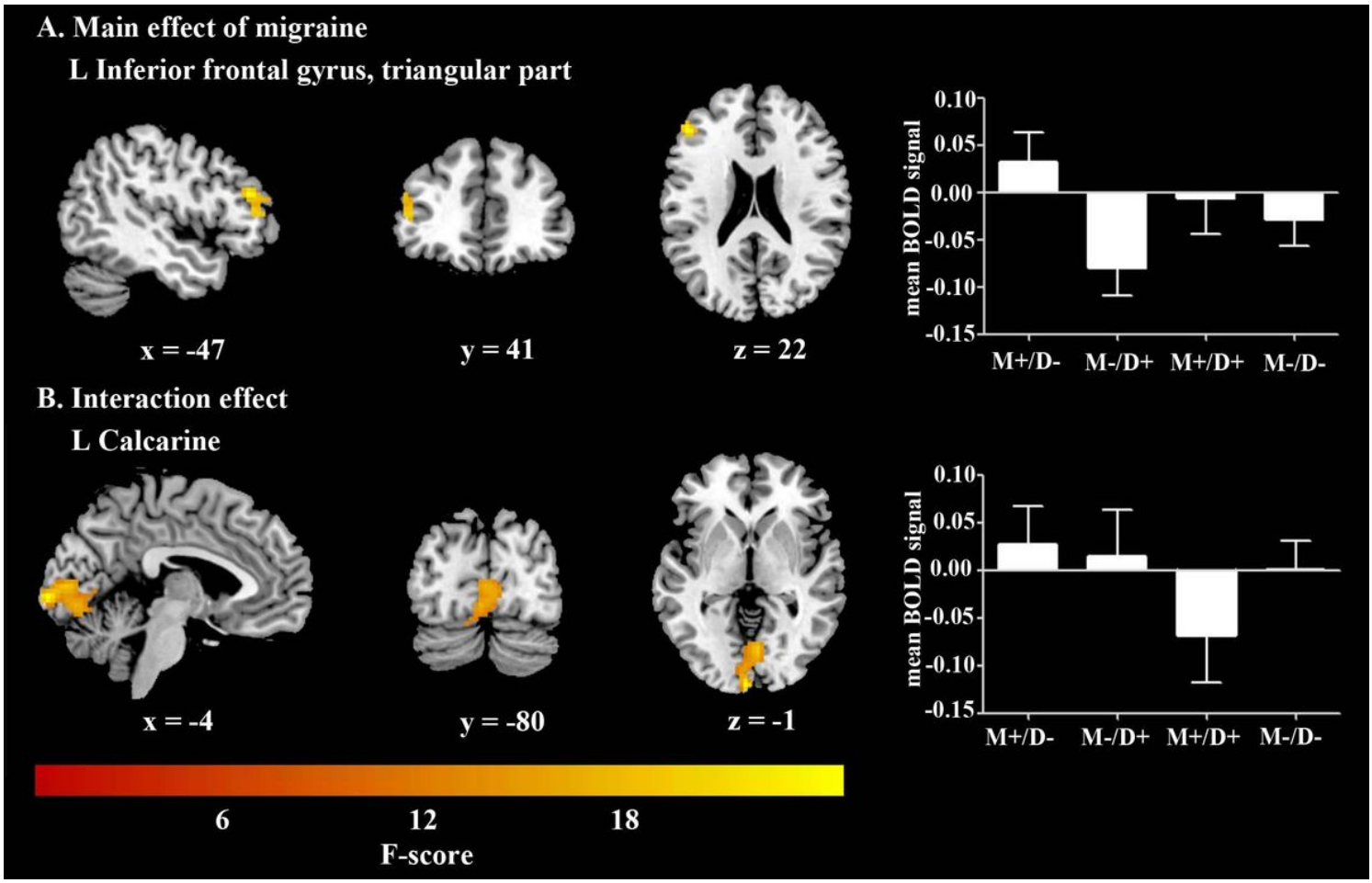

## Figure 2

One-way ANOVA analysis on fALFF among the four groups. Significant group differences in the left mPFC (including the superior frontal gyrus, medial and superior frontal gyrus). On the right, the histograms exhibited the mean fALFF value by group (error bars represents standard error from mean) in each identified ROI. Abbreviations: fALFF, fractional amplitude of low-frequency fluctuations; ROI, region of interest; M+/D+, migraineurs with depression; M+/D-, migraineurs without depression; M-/D+, patients with major depressive disorder; M-/D-, healthy controls; L, left. * P < 0.05 (Bonfornni corrected).



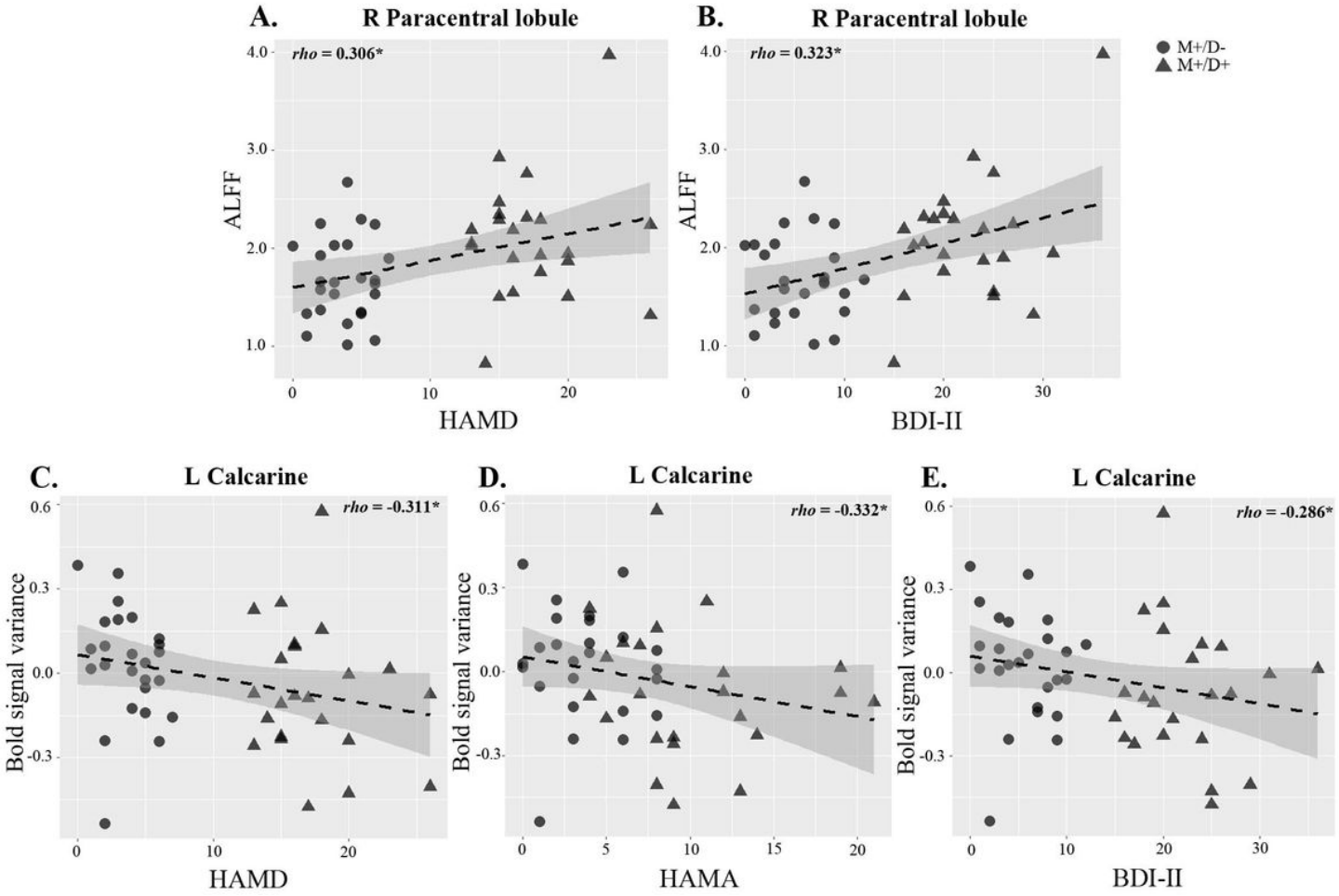

## Figure 3

One-way ANOVA analysis on ReHo among the four groups. Significant group differences in the left inferior occipital gyrus, the left calcarine, the left mPFC (the superior frontal gyrus, medial), and the right lingual. On the right, the histograms exhibited the mean ReHo value by group (error bars represents standard error from mean) in each identified ROI. Abbreviations: ReHo, regional homogeneity; ROI, region of interest; M+/D+, migraineurs with depression; M+/D-, migraineurs without depression; M-/D+, patients with major depressive disorder; M-/D-, healthy controls; L, left; R, right. * P < 0.05 (Bonfornni corrected).




## Figure 4

Two-way ANOVA analysis on brain function among the four groups. (A) Significant main effect of migraine in the left inferior frontal gyrus, triangular part. (B) Significant interaction effects between migraine and depression in the left calcarine. On the right, the histogram exhibited the mean Bold signal by group (error bars represents standard error from mean). Abbreviations: M+/D+, migraineurs with depression; M+/D-, migraineurs without depression; M-/D+, patients with major depressive disorder; M-/D-, healthy controls; L, left.




## Figure 5

Scatter plots of correlations between brain function and clinical variables in the M+ patients. /D+ and /D- groups are shown separately. (A, B) Positive correlations between ALFF value and HAMD, BDI-II. (C, D, E) Negative correlations between BOLD signal variance and HAMD, HAMA, and BDI-II. Abbreviations: ALFF, amplitude of low-frequency fluctuations; rho, spearman correlation coefficient; HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; BDI-II, Beck Depression inventory-II; M+/D-, migraineurs without depression; M+/D+, migraineurs with major depressive disorder; L, left; R, right. *P < 0.05.