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ORIGINAL PAPER

Sex differences in anhedonia in bipolar depression: a resting-state fMRI study

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Abstract

Previous studies about anhedonia symptoms in bipolar depression (BD) ignored the unique role of gender on brain function. This study aims to explore the regional brain neuroimaging features of BD with anhedonia and the sex differences in these patients. The resting-fMRI by applying fractional amplitude of low-frequency fluctuation (fALFF) method was estimated in 263 patients with BD (174 high anhedonia [HA], 89 low anhedonia [LA]) and 213 healthy controls. The effects of two different factors in patients with BD were analyzed using a 3 (group: HA, LA, HC) × 2 (sex: male, female) ANOVA. The fALFF values were higher in the HA group than in the LA group in the right medial cingulate gyrus and supplementary motor area. For the sex-by-group interaction, the fALFF values of the right hippocampus, left medial occipital gyrus, right insula, and bilateral medial cingulate gyrus were significantly higher in HA males than in LA males but not females. These results suggested that the pattern of high activation could be a marker of anhedonia symptoms in BD males, and the sex differences should be considered in future studies of BD with anhedonia symptoms.

Keywords Bipolar depression · Anhedonia · Sex difference · Functional neuroimaging · Hippocampus · Insula

Introduction

Psychologically, wanting, liking, and learning have been identified as three important dissociable components of reward [2], and the neural network underpinning these aspects of reward processing is closely related to anhedonia symptoms [59, 61]. Patients with anhedonia symptoms often report difficulty experiencing normally positive events as pleasurable or deficits in motivation to pursue rewards [47]. The importance of anhedonia has been evidenced by its prevalence, poor long-term outcomes [9, 31], and association with high levels of suicidal ideation in psychiatric patients [3].

As a cross-diagnostic symptom, anhedonia is found in depression states of major depressive disorder and bipolar disorder, as well as other disorders. More than half of patients with bipolar depression (BD) suffer from anhedonia [12, 30, 52]. The application of neuroimaging techniques in psychiatric disorders helps us understand the neural mechanism of anhedonia symptoms in BD patients. A task-related functional magnetic resonance imaging (fMRI) study tested the brain activity associated with reward processing. The results showed that BD had low activation of the nucleus accumbens (NAc), caudate nucleus, thalamus, putamen, insula, and prefrontal areas in the reward condition [43]. Another study found that BD patients with anhedonia symptoms shared decreased structural covariance of NAc connected to the prefrontal gyrus and bilateral striatum, extending to the bilateral anterior insula and increased structural covariance of NAc connected to the left hippocampus extending to the thalamus [23]. In a study of youth with

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BD, anhedonia was inversely correlated with global cerebral blood flow in the anterior cingulate cortex (ACC) [13]. Although the conclusion is not entirely consistent, the dysfunction of the reward-related regions in BD has been widely described.

However, past studies about anhedonia symptoms in BD ignored the unique role of gender in the reward-related regions. An fMRI study demonstrated that the abnormal functional patterns in the hippocampus, right amygdala, left caudate, and prefrontal cortex (PFC) regions differ between male and female patients with BD [25]. A study reported that male patients with BD showed greater vermis and caudate volumes than male healthy controls (HC), while female patients with BD did not show significant differences [55]. Another study found that the right subcallosal limbic ACC thickness was higher in men with BD than in controls [17]. Compared to male patients with BD, female patients with BD present with smaller right hippocampal volumes [45]. A recent study reported that sex moderates frontostriatal volume in bipolar spectrum disorders. Enlarged volume in the medial orbitofrontal cortex and NAc may reflect a marker of risk for bipolar spectrum disorders in males [10]. Overall, past evidence points to an important role of gender in reward-related regions.

Although no clinical studies have reported sex differences in the manner or severity of anhedonia in BD patients, the performance of mice with anhedonia in terms of desire for sexual activity, foraging, and parental behavior is sexually dimorphic [46]. A recent animal study found that anhedonic behavior in mice shows sexual dimorphism, which is mediated by the ventral hippocampus–NAc pathway [53]. Another study proposed that the discrepancies in anhedonia behavior between male and female mice may be caused by an imbalance in microglial activation in the hippocampus [28]. These preclinical studies add to the evidence that there are gender differences in reward-related regions underlying anhedonia symptoms.

In this study, the role of sex differences in the reward circuit was considered when investigating the brain functional characteristics in bipolar disorder with anhedonia symptoms. We aim to explore the sex differences in regional brain neuroimaging activity features in BD patients with high anhedonia symptoms. We proposed that neural functional characteristics in patients with BD and anhedonia symptoms may be sexually dimorphic.

The fMRI technology can show changes in magnetic resonance signals due to the oxygenation status of the blood in the venous capillaries in various brain regions [49]. It has been shown that the spontaneous low frequency (0.01–0.08 HZ) fluctuations in the blood oxygen level-dependent (BOLD) fMRI signal at rest are physiologically meaningful, representing local brain glucose metabolism [29] and related to the intensity of regional spontaneous neuronal activity [63]. The amplitude of low-frequency fluctuations (ALFF) is a quantitative method to measure the regional intensity of spontaneous neuronal fluctuations in the BOLD time course [58]. The ALFF approach has been increasingly employed to assess the pathological brain activity in many diseases, such as schizophrenia[20] and major depression disorder[50], all showing that ALFF is a reliable and sensitive way to locate dysfunctional brain regions related to symptom (such as anhedonia) in neuropsychiatric disorders (such as MDD). Compared with ALFF, the fractional amplitude of low-frequency fluctuations (fALFF) can effectively suppress the non-specific signal components in rsfMRI, and this will significantly improve the sensitivity and specificity of detecting regional spontaneous brain activity [62, 63]. Therefore, this study used this potential biomarker reflecting regional spontaneous brain activity to explore whether there are sex differences in the spontaneous brain activity of BD patients with anhedonia symptoms in the resting state. We calculated the differences in spontaneous activity in BD patients with anhedonia symptoms, and we hypothesized that neuroimaging findings in reward-related brain areas are different in male and female BD patients with anhedonia.

Materials and methods

Participants

Between February 2015 and December 2021, patients with BD were enrolled from inpatients of the Affiliated Nanjing Brain Hospital of Nanjing Medical University. The following were the inclusion criteria for the participants: (1) BD diagnosis was confirmed using DSM-V criteria, and the participant suffering from a current depressive episode; (2) right-handedness; (3) an education level of junior school or higher; (4) aged between 18 and 50 years old; (5) Chinese Han; (6) a 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) [22] score > 17; (7) a Montgomery-Asberg Depression Rating Scale (MADRS) [34] ≥ 25. The exclusion criteria were as follows: (1) any other pertinent medical or mental problem other than BD psychopathology; (2) a history of systemic illness; (3) current pregnancy or breastfeeding; (4) substance abuse or dependence; (5) any physical therapy such as repetitive transcranial magnetic stimulation (rTMS) within the previous six months before the scan; (6) any contraindications to MRI scanning; and (7) sex-transitioned population or patients with gender identity disorder. The inclusion criteria for the HC group were as follows: (1) screened to have no BD using the DSM-V nonpatient version of the Structured Clinical Interview; (2) right-handedness; (3) aged between 18 and 50 years old; (4) junior school or higher education level; (5) Chinese Han; (6) a $HAMD_{17}$

score < 7; (7) no neurological illness or mental illness; and (8) no family history of neurological or psychiatric illness.

Finally, 263 patients with BD were assigned to two groups depending on their MADRS item 8 score. Patients with a MADRS item 8 score [11, 12] ≥ 3 were grouped into the high anhedonia (HA) group (n = 174), whereas patients with a MADRS item 8 ≤ 2 were grouped into the low anhedonia (LA) group (n = 89). Using local hospital marketing and word-of-mouth, 213 HC matched in age, sex, and education level were enrolled.

After thoroughly explaining all the details of the research to all the participating individuals, formal informed consent was obtained. The Research Ethics Review Board of the Affiliated Nanjing Brain Hospital of Nanjing Medical University authorized this experiment.

MRI scan acquisitions

The imaging data were acquired using a 3-Tesla Siemens Verio scanner with an eight-channel radio frequency coil in the Nanjing Brain Hospital. All the participants were placed in a birdcage head coil fitted with foam padding to reduce head motion. The participants were instructed to lie quietly on the examination bed, close their eyes, keep their heads fixed, avoid overthinking, stay awake, and raise hands if feeling any discomfort during the scan. During the scan, the patient's head movement was monitored. At the end of the MRI scan, patients were asked if they fell asleep and overthought.

The settings of the T1 anatomic axial imaging and echo-planar imaging were the same as in previous papers[56]. The parameters for the T1 anatomic axial imaging were as follows: repetition time (TR) = 1900 ms, echo time (TE) = 2.48 ms, flip angle (FA) = 9°, number of slices = 176, slice thickness = 1 mm, in-plane voxel resolution = 1 × 1 mm, and field of view (FOV) = 25 × 25 cm^2. Resting-state fMRI data were obtained using an echo-planar imaging (EPI) sequence. The parameters were as follows: TE = 40 ms, TR = 3000 ms, FA = 90°, slice thickness = 4 mm, slice gap = 4 mm, number of slices = 32, FOV = 24 × 24 cm^2, matrix size = 64 × 64, in plane voxel resolution = 3.75 × 3.75 mm, and volume number = 133.

Data pre-processing

The Data Processing Assistant for Resting-State fMRI (DPARSF; http://rfmri.org/DPARSF) was used to analyze the functional imaging data [8]. The first six functional volumes were removed to allow the participants to adapt to the scanner noise. The slices were timed, and the head motion was corrected. Subsequently, spatial normalization of the Montreal Neurological Institute (MNI) space was performed. The resample voxel size was 3 x 3 x 3 mm^3. These steps were the same as in our prior study [56].

Participants were excluded when their head rotation angle was > 2° or when their head movement was > 2 mm to assure data reliability. We eliminated various sources of variation, including head-motion characteristics, averaged global BOLD signals, and mean BOLD signals in the ventricular and white matter areas. The framewise displacement of the rigid body-motion correction process was utilized to construct an estimate of head motion at each time point [40]. Head motion effects detected by the Friston 24-parameter model were removed as nuisance variables [18]. The structural images were standardized to the MNI template (T1-weighted). Following this, the data were smoothed with a 4 mm Gaussian kernel with a full width at half maximum (FWHM). Finally, low-frequency drift was reduced using linear detrending, and high-frequency noise was reduced by temporal filtering (0.01–0.08 Hz).

fALFF analysis

The participants' fALFF values were obtained using the DPABI software package. The preprocessed time series of each voxel was transformed into the frequency domain based on a fast Fourier transformation. The square root of each frequency was then calculated in the power spectrum to obtain the average square root at a low-frequency range (0.01–0.08 Hz). Thus, fALFF was acquired by comparing the ratio of the power spectrum of low-frequency (0.01–0.08 Hz) to the entire frequency range.

Statistical analyzes

The sex distributions among the six groups (male with high anhedonia, female with high anhedonia, male with low anhedonia, female with low anhedonia, healthy male, and healthy female) were examined using a two-tailed Pearson's chi-square test, and a one-way analysis of variance (ANOVA) was employed to assess the distributions of age and years of education. The age of onset, illness duration, number of episodes, MADRS item 8 scores, and total $HAMD_{17}$ and MADRS scores among the four groups of patients with BD (males with high anhedonia, females with high anhedonia, male with low anhedonia, female with low anhedonia) were compared using a one-way ANOVA. A two-sample two-tailed t-test was used to compare the MADRS item 8 scores and the total $HAMD_{17}$ and MADRS scores of males and females in the HA group and LA group. In addition, considering that men and women have different rates of brain development [38], they have different levels of vulnerability to disease. We used a two-sample t-test to analyze the difference in age of onset of

BD between males and females. These statistical analyses were conducted using SPSS 25.0 software (IBM Corp., Armonk, NY, USA).

To parse out the effects of sex and anhedonia on patients with BD, we entered all of the voxel-based comparisons of the whole brain into a 3 (HA, LA, HC) × 2 (male, female) analysis of variance (ANOVA) model in the Statistical Parametric Mapping (SPM12) software (www.fl.ion.ucl.ac.uk/spm/; Gaussian random field [GRF] correction; voxel size, $p < 0.001$; cluster size, $p < 0.05$). Concurrently, the MADRS except for item 8 scores were taken as covariates.

For illustration of our final results, we extracted the fALFF values in the peak coordinates of brain regions with significant sex (male, female) effect, groups effect (HA, LA, HC), and interaction effect (sex × group) to perform further simple analysis in SPSS 25.0 software. We used the FDR correction for the multiple comparison.

Results

Demographic and clinical characteristics

This research included 263 patients with BD, with 174 patients in the HA group (77 males, 97 females), and 89 patients in the LA group (26 males, 63 females). Overall, 213 HC participants were recruited. To compare the groups regarding sociodemographic characteristics, SPSS 25.0 software was utilized. There were no statistically significant differences among the six groups regarding age and no discernible difference in the illness progression, the overall $HAMD_{17}$ and MADRS scores among the four patient groups ($p > 0.05$). Further information is presented in Table 1.

3×2 ANOVA

Regarding the group effect (HA, LA, and HC), the fALFF values were significantly difference in the right superior temporal pole, left inferior occipital gyrus, right STG, right SFG

Table 1 Demographic and clinical characteristics grouped by sex

Variables	High anhedonia		Low anhedonia		Healthy controls		*t/F/χ*	*p*
	Male	Female	Male	Female	Male	Female		
number	77	97	26	63	93	120	6.482	0.039*[a]
Age, y	30.69±9.71	28.43±9.04	27.19±9.20	27.44±8.32	30.22±7.60	29.85±7.80	1.849	0.102[b]
Education, y	13.99±2.83	13.64±2.71	13.73±2.88	15.08±2.20	15.45±1.89	15.58±2.12	11.417	0.000*[b]
Depression, No. of episodes	3.12±2.41	2.90±2.56	1.92±3.43	3.43±1.94			2.434	0.067[b]
Duration of illness, mo	68.63±85.24	53.90±62.05	58.33±39.62	49.55±50.81			0.702	0.552[b]
Current duration of illness, mo	13.91±30.66	14.47±46.66	10.98±6.21	17.79±38.54			0.184	0.907[b]
Effective duration of illness, mo	21.37±33.44	26.67±40.90	22.94±7.91	21.78±25.04			0.166	0.919[b]
hospitalized times	1.24±0.57	1.13±0.47	1.28±0.28	1.25±1.10			0.577	0.631[b]
Age of onset, y	26.53±9.04	25.74±10.20	22.33±8.99	23.28±8.11			1.683[b] 0.072[c]	0.173[b] 0.788[c]
$HAMD_{17}$ total score	23.11±5.04	22.88±5.13	22.15±2.09	21.57±2.08			1.711	0.166[b]
MADRS total score	32.96±5.11	32.62±4.25	30.42±4.68	28.29±4.42			2.279	0.080[b]
$MADRS_8$ score	4.51±0.91	4.55±0.91	0.92±0.80	0.98±0.71			339.40[b] 0.286[d1] 0.357[d2]	0.000*[b] 0.775[d1] 0.722[d2]
Marriage(married/unmarried/divorced)	45/29/3	43/47/7	7/17/2	19/43/1	21/71/1	38/81/1		
Family history(no/yes)	55/22	69/28	17/9	39/24	93/0	120/0		

Participants self-identified as Asian (100%)

Data were presented as the range of minimum-maximum (mean±SD)

$HAMD_{17}$ 17-item of Hamilton Depression Rating Scale; *MADRS* Montgomery-Asberg Depression Rating Scale; *y* = year; *mo* = month.

[a]The *p* value was obtained by a two-tailed Pearson chi-square *t* test.

[b]The *F/p* value was obtained by one-way analysis of variance.

[c]The *p* value was obtained by a two-sample two-tailed t-test between males and females in BD patients.

[d1]The *p* value was obtained by a two-sample two-tailed t-test between males and females in high anhedonia group.

[d2]The value was obtained by a two-sample two-tailed t-test between males and females in low anhedonia group

pars orbital, right precuneus, left angular, right middle cingulum gyrus (MCG), left supplementary motor area (SMA), left middle frontal gyrus (MFG) (Table 2 and Fig. 1A). A simple post hoc analysis shows that the fALFF values of right MCG and left SMA ($p < 0.001$, FDR corrected) were significantly higher in the HA group than in LA (Table 3 and Fig. 2A).

In terms of the sex effect (male, female), the fALFF values were significantly different in the left insula, right rolandic operculum, right superior temporal gyrus (STG), left calcarine, left medial superior frontal gyrus (SFG), and right SMA (Table 2, Fig. 1B, and Fig. 2B).

For the sex-by-group interaction, there were significant differences in the fALFF values among the six groups in the right hippocampus, left medial occipital gyrus, right insula, and bilateral MCG (Table 2 and Fig. 1C). A simple post hoc analysis shows that the fALFF values of all these regions were significantly higher in the HA group than LA in male patients ($p < 0.001$, FDR corrected). The fALFF values of the right hippocampus ($p < 0.001$, FDR corrected) were significantly lower in the HA group than LA in female patients (Table 3 and Fig. 2C).

Table 2 Results of the 3 (Group: HA, LA, HC) × 2 (sex: male, female) ANOVA

	MNI			Cluster size	*F*/*t* -value
	x	y	z		
GROUP					
Temporal_Pole_Sup_R	51	12	−18	76	15.0705
Occipital_Inf_L	−33	−69	−6	2389	26.5582
Temporal_Sup_R	45	−24	0	1263	24.6243
Frontal_Sup_Orb_R	24	42	−12	78	15.5815
Precuneus_R	9	−78	54	887	24.6681
Angular_L	−48	−72	33	104	14.7488
Cingulum_Mid_R	12	21	39	52	15.6711
Supp_Motor_Area_L	−9	3	54	244	15.5501
Frontal_Mid_L	−30	30	51	109	12.4985
SEX					
Insula_L	−39	3	9	643	47.3963
Rolandic_Oper_R	54	0	9	371	33.7026
Temporal_Sup_R	60	−24	3	37	18.5378
Calcarine_L	−15	−57	12	48	24.3773
Frontal_Sup_Medial_L	−3	42	21	180	22.5926
Supp_Motor_Area_R	6	3	63	105	20.231
GROUP × SEX					
Hippocampus_R	21	−18	−12	46	19.4273
Occipital_Mid_L	−36	−72	3	53	15.5853
Insula_R	33	−18	18	111	24.041
Cingulum_Mid_R	9	−9	36	43	14.4411
Cingulum_Mid_L	−15	−33	51	35	12.7886

HA high anhedonia; *LA* low anhedonia; *HC* health controls; *MNI* Montreal Neurological Institute; x, y, z are the coordinates of the primary peak locations in the MNI space; *L* = left; *R* = right; *Mid* = middle; *Sup* = superior; *Supp* = supplementary; *Inf* = inferior; *Oper* = operculum; *Orb* = orbital

F is obtained by one-way analysis of variance

t is obtained by a two-sample two-tailed t test (GRF correction; voxel size $p < 0.001$; cluster size $p < 0.05$)

Discussion

In this study, we found that the fALFF values of the right MCG and left SMA were significantly higher in the HA group than in LA, and the left insula, right rolandic operculum, right STG, left calcarine, left medial SFG, and right SMA were higher in males than females. The fALFF values of the right hippocampus, left medial occipital gyrus, right insula, and bilateral MCG were significantly higher in the HA group than in LA in male patients. In contrast, the right hippocampus was lower in the HA than in LA in female patients. This study provides some implications for the sex differences in neuropathological mechanisms of anhedonia symptoms in BD.

Enhanced fALFF values in MCG and SMA are consistent with previous studies on reward-related brain dysfunction associated with anhedonia symptoms. The MCG guides reward-based decision-making [54]. Specifically, the MCG learns to obtain goals based on the outcomes, rewards, and punishments received for different actions [26, 54]. The SMA plays a vital role in motor planning and execution of voluntary movements and in somatosensory processing, being part of the sensorimotor network [44]. Dysfunctional activity in the SMA has been related to alterations in body perception [21]. Some studies found that the SMA has often been activated along with the cingulate gyrus in reward task-based fMRI studies, particularly during the anticipation/decision phase of reward [6, 33]. This study found that the high fALFF values in the MCG and SMA can be seen as the brain markers of the anhedonia symptoms in BD.

The gender differences in the brain manifest in various aspects across brain structure, function, molecular, and behaviors [1, 60]. This study found higher fALFF values in the left insula, right rolandic operculum, right STG, left calcarine, left medial SFG, and right SMA in males than in females. For example, the SFG, as an advanced supervisory system [15, 41], is one of the final brain areas to develop [14]. Previous studies have reported that the SFG exits sex differences in development rates, with earlier maturation apparent in females compared to males [19, 38]. Our results focused on frontal and temporal-limbic system regions, which are closely associated with processes such as the subjective experience of emotion, cognitive appraisal, and control, demonstrating functional differences in neural circuits between males and females.

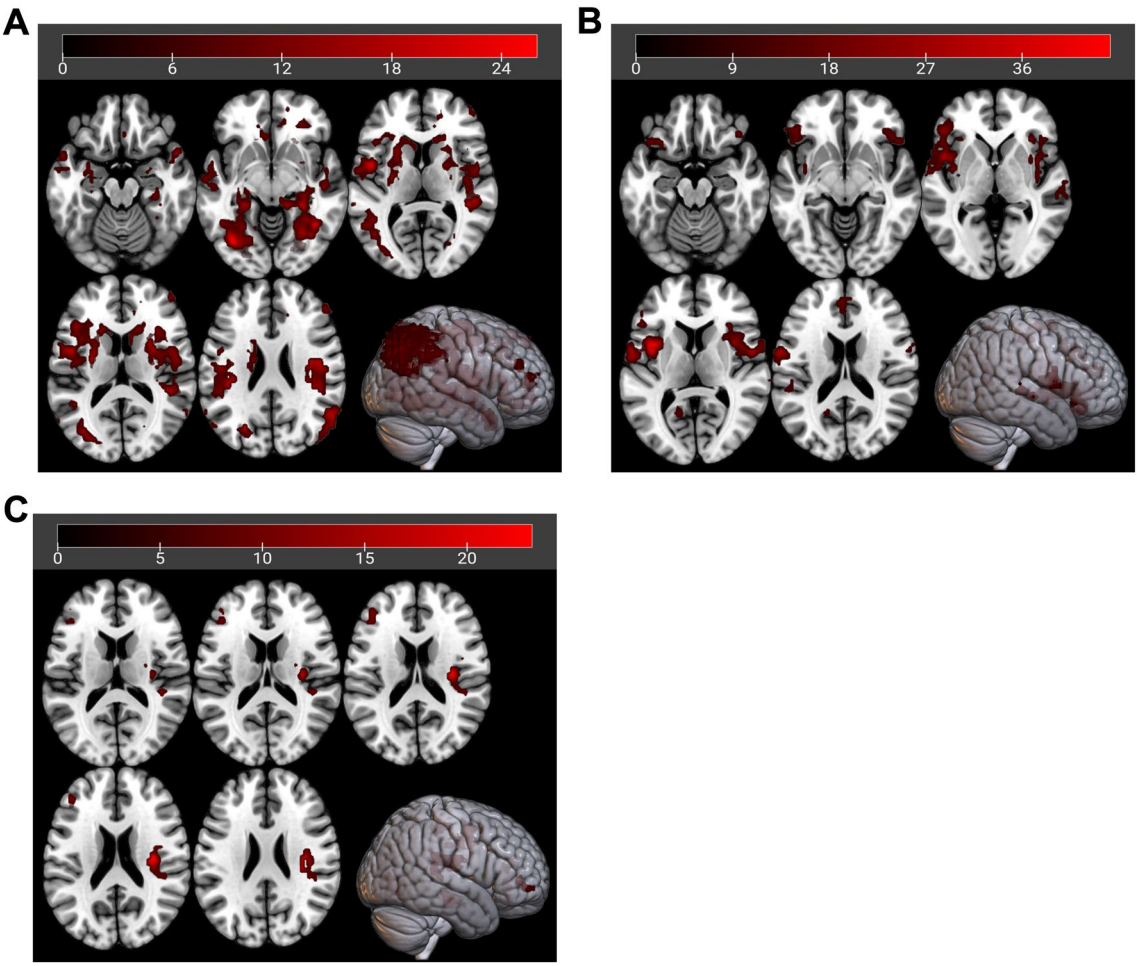

Fig. 1 Brain areas with significantly different after 3 (HA, LA, HC) × 2 (male, female) ANOVA. **A** Brain regions showing the fALFF differences in patients with BD by the group (HA, LA) effects. **B** Brain regions showing the fALFF in patients with BD by the sex (male, female) effects. **C** Brain regions showing the fALFF differences between male and female BD patients by the sex-by-group interaction effects. (voxel $p < 0.001$, cluster $p < 0.05$, GRF corrected)

Notably, multiple evolutionary, genetic, and environmental factors may produce sex differences in the brain function in BD [42, 57], potentially supported by the documented sex differences in the illness course and clinical presentation [5, 32]. The present study found an interaction effect among the six groups (male with HA, female with HA, male with LA, female with LA, healthy male, and healthy female). The fALFF values were higher in the right hippocampus, left medial occipital gyrus, right insula, and bilateral MCG in male patients with HA than in LA. In contrast, this phenomenon was not observed in female patients. Similar to previous research about sex differences in BD [10, 16, 25], our results were also concentrated in limbic reward-related regions.

A recent study showed that male patients with BD had higher fALFF in the right hippocampus than controls [25]. Our results demonstrated that this abnormally high activity may relate to the anhedonia symptoms. Past studies on anhedonia have highlighted the importance of NAc. As a hedonic hot spot, NAc is implicated in the hedonic experience and reward processing per se [39]. Recently, the link between the hippocampus and anhedonia symptoms has been elucidated in several studies [4, 7, 48]. Indeed, hippocampal input to the shell of the NAc is essential for driving NAc activity, and the activity-dependent modulation of the strength of this input may play a role in the proper regulation of goal-directed behaviors [27]. Anhedonia-like behavior in mice, associated with the ventral hippocampal-NAc pathway, differed between the sexes [53]. This study identified the abnormal higher functional activation in the hippocampal brain region of male patients in HA than in LA.

The insula is the key cortical node of the interoceptive system and is linked to natural rewards, thereby encoding interoceptive information to sustain goal-directed behavior [36]. The insula plays a role in receiving and integrating information from the hippocampus, cingulum,

Table 3 A simple post hoc analysis in brain regions with significant interaction effects

	SEX	*p* (HA vs LA)	*p* (HA vs HC)	*p* (HC vs LA)
GEOUP				
Temporal_Pole_Sup_R		0.608862	0.000012***	0.002368
Occipital_Inf_L		0.011440	1.9865e–14***	0.000181***
Temporal_Sup_R		0.005196	6.9323e–15***	0.000331***
Frontal_Sup_Orb_R		0.033385	6.6434e–9***	0.010173
Precuneus_R		0.004164	1.7268e–12***	0.003951
Angular_L		0.002791	5.0e–7***	0.306621
Cingulum_Mid_R		5.8435e–7***	0.000002***	0.182334
Supp_Motor_Area_L		0.000001***	4.3612e–7***	0.358749
Frontal_Mid_L		0.099428	1.355e–7***	0.008837
GROUP × SEX				
Hippocampus_R	Male	0.000103***	3.446e–10***	1.000000
	Female	1.6826e–9***	0.472251	4.2549–7***
Occipital_Mid_L	Male	3.4752e–11***	3.6802e–8***	0.006414
	Female	1.000000	0.321535	0.004679
Insula_R	Male	6.8257e-14***	8.1674e–12***	0.006777
	Female	0.056423	1.000000	0.011585
Cingulum_Mid_R	Male	0.000001***	0.000006***	0.176368
	Female	0.145598	1.000000	0.019701
Cingulum_Mid_L	Male	0.000005***	2.4277e–9***	1.000000
	Female	0.144957	1.000000	0.041117

HA high anhedonia; *LA* low anhedonia; *HC* health controls; *L* = left; *R* = right; *Mid* = middle; *Sup* = superior; *Supp* = supplementary; *Inf* = inferior; *Oper* = operculum; *Orb* = orbital

p is obtained by post hoc *t* test (FDR correction), ***$p < 0.001$

and other limbic systems. The cingulum helps the insula participate in interoception processes and regulates cognition, attention, and emotion [26]. A meta-analysis of reward-related research shows that decreased insula activation is associated with abnormal reward consumption [51]. During an emotional facial recognition task, a fMRI study showed a negative correlation between anhedonia severity and anterior insula and cingulum activation during positive emotional stimulation [24]. The overactivation in the resting state might reflect either compensatory recruitment of these regions to facilitate emotional regulation or aberrant appraisal and heightened emotional experience in daily life. This pattern of high brain activation could be a marker of anhedonia symptoms in BD males, which is a sign of a compensatory mechanism, or overactivity could be directly pathological. Patients with BD and anhedonia show dysregulated internal monitoring of emotions and difficulties identifying and processing positive emotions. Extending prior work, our exploratory analyses suggest that the high fALFF values of the insula and hippocampal in BD with HA may be specific to males.

Limitations

Unfortunately, this study has some shortcomings that need to be considered. First, most of the inpatients included in this study have been treated with drugs, so the interference of drugs in this experiment cannot be excluded. In the future, more drug-free patients should be included for additional investigation. Second, we did not divide the patients with BD into type I BD and type II BD. And, using item 8 of the MADRS scale to assess anhedonia symptoms was not sufficient. Third, the MRI scan section collected less than seven minutes of resting state and closed eyes during fMRI scanning [37]. That should be the limitation as well. We also used the global signal regression (GSR), a controversial method [35]. However, there is no single "right" way to process resting-state data that reveals the "true" nature of the brain. Although further work is needed, different processing approaches likely reveal complementary insights about the brain's functional organization. Finally, as this was a cross-sectional study, we could not establish causal links between BD

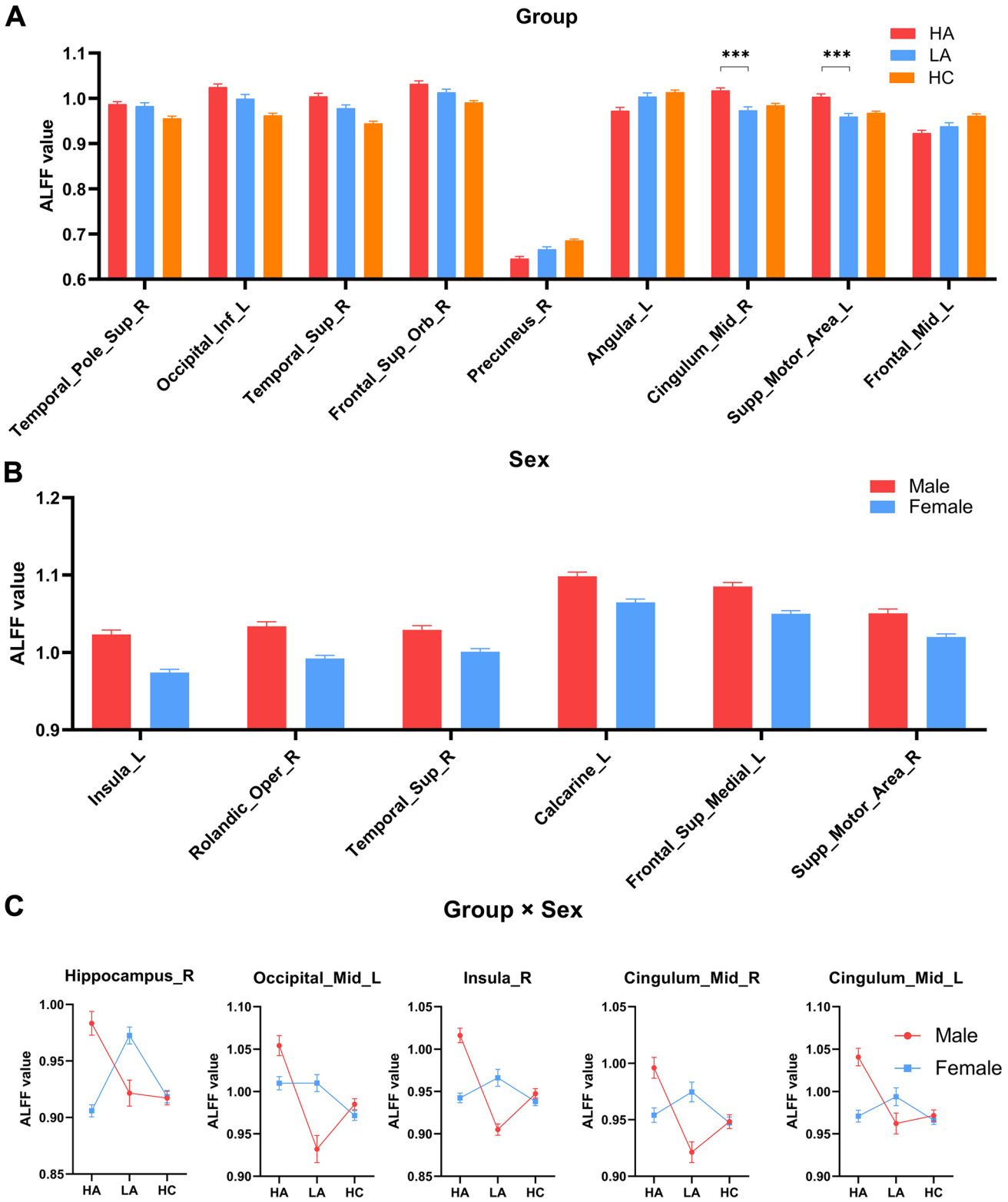

Fig. 2 Schematic diagram of main effects of sex, group, and sex-by-group interaction on the fALFF values among the six groups. **A** The differences of the fALFF values for the main effect of group (HA, LA, and HC). **B** The differences of the fALFF values for the main effect of sex (male, female). **C** The differences of the fALFF values for the sex-by-group interaction effects. (***$p < 0.001$, FDR corrected)

and functional alterations in the brain, and longitudinal research might provide more insight into this issue.

Conclusion

In this study, we identified abnormal fALFF activation in limbic reward-related regions in patients with BD and anhedonia. Moreover, our findings identified a unique role of gender in the neural mechanism of anhedonia. High activation in the right hippocampus, left medial occipital gyrus, right insula, and bilateral MCG is related to high anhedonia in males but not females. Our results suggest the need to emphasize gender specificity in clinical work and scientific research about anhedonia symptoms.

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Author contributions Zhijian Yao and Qing Lu designed the study, wrote the protocol, and revised the paper. Xiaoqin Wang and Yi Xia managed the literature research, analyzed and wrote the first draft of the manuscript. Yinghong Huang and Rui Yan collected experimental data and prepared Table 1. Hao Sun, Qiudong Xia, and Junling Sheng analyzed the results and made Tables 2 and 3. Wei You analyzed the results and prepared Figure 1. Lingling Hua and Hao Tang analyzed the results and prepared Figure 2. All authors reviewed the manuscript and have approved the final manuscript.

Data availability This study guarantees the data's authenticity and availability, but considering patients' privacy, the data will not be disclosed to the public.

Declarations

Conflict of interest The authors declare that no competing interests exist. All authors disclosed no relevant relationships.

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