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Aberrant interhemispheric functional connectivity in major depressive disorder with and without anhedonia

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Abstract

Objective: Anhedonia is a core feature of major depressive disorder (MDD), and as a subtype of depression, MDD with anhedonia may have exceptional neurobiological mechanisms. However, the neuropathology of anhedonia in MDD remains unclear. Thus, this study aimed to investigate the brain functional differences between MDD with and without anhedonia.

Methods: A total of 62 individuals including 22 MDD patients with anhedonia, 20 MDD patients without anhedonia, and 20 healthy controls (HCs) were recruited for this study. All participants underwent 3.0-T functional magnetic resonance imaging scan. Voxel-mirrored homotopic connectivity (VMHC) was employed to quantitatively describe bilateral functional connectivity. Analyses of variance (ANOVA) were performed to obtain brain regions with significant differences among three groups and then post hoc tests were calculated for inter-group comparisons.

Results: The ANOVA revealed significant VMHC differences among three groups in the bilateral middle temporal gyrus (MTG), superior frontal gyrus (SFG), and inferior parietal lobule (IPL) ($F = 10.47 \sim 15.09$, $p < 0.05$, *AlphaSim corrected*). Relative to HCs, MDD with anhedonia showed significantly decreased VMHC in the bilateral MTG ($t = -5.368$, $p < 0.05$, *AlphaSim corrected*), as well as increased VMHC in the bilateral SFG ($t = -4.696$, $p < 0.05$, *AlphaSim corrected*). Compared to MDD without anhedonia, MDD with anhedonia showed significantly decreased VMHC in the bilateral MTG and IPL ($t = -5.629 \sim -4.330$, $p < 0.05$, *AlphaSim corrected*), while increased VMHC in the bilateral SFG ($t = 3.926$, $p < 0.05$, *AlphaSim corrected*). However, no significant difference was found between MDD without anhedonia and HCs.

Conclusion: The present findings suggest that MDD with and without anhedonia exhibit different patterns of interhemispheric connectivity. Anhedonia in MDD is related to aberrant interhemispheric connectivity within brain regions involved in the frontal-temporal-parietal circuit.

Keywords: Major depressive disorder, Anhedonia, Functional magnetic resonance imaging, Voxel-mirrored homotopic connectivity

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Introduction

Major depressive disorder (MDD) is a highly heterogeneous and etiologically complex psychiatric disorder, involving a broad spectrum of psychopathology from distinct pathophysiological mechanisms [1]. Different subtypes of depression are being distinguished in the



literature, among which MDD with anhedonia has drawn more and more attention in recent years [2]. Anhedonia, which used to define as a “loss of pleasure”, now reflects a broader conceptualization that includes interest and consummatory pleasure according to the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)* [3]. It has been reported that MDD with anhedonia is associated with greater severity of depressive episodes, more likelihood of psychotic symptoms, and increased suicidality [4, 5]. Moreover, it has been revealed that anhedonia in MDD predicts poorer response to pharmacological treatments for depression and poorer long-term outcomes [6, 7]. Despite the importance of anhedonia for the diagnosis and prognosis of MDD, the neural mechanisms associated with anhedonia in MDD are poorly understood.

Over a few decades, it has been suggested that clinically relevant differences in the underlying pathophysiology in patients with MDD exist [8]. In particular, as a core feature of MDD, the identification of anhedonia endophenotype for MDD may improve our understanding of the disease. Consequently, previous studies have revealed that distinct alterations of the hypothalamic–pituitary–adrenal (HPA) axis activity [9], inflammatory characteristics [10], gut microbiota abundance [11], and metabolism of brain-derived neurotrophic factor (BDNF) [12] may play a critical role for MDD patients with and without anhedonia. Taken together, these findings suggest that anhedonia in MDD may have exceptional neurobiological mechanisms and highlight the importance of studies that focus on the effect of anhedonia on biological changes in MDD.

In recent years, noninvasive neuroimaging technique like functional magnetic resonance imaging (fMRI) has been utilized to discover neurobiological underpinnings of psychiatric disorders [13]. Simultaneously, significant efforts have been made to understand the neuroimaging characteristics of anhedonia in MDD. It has been revealed that aberrant striatal and ventral striatal activity and frontostriatal connectivity abnormalities are most frequently associated with the subjective report of anhedonia [2, 14]. Nevertheless, most of these studies investigated the neural basis of anhedonia using correlation analyses of neurocircuitry with self-reported anhedonia scores [15, 16]. In addition, the majority of previous neuroimaging findings concerning anhedonia were provided by task-based fMRI studies probing reward processing [17]. It is acknowledged that task-related alterations in neural activation may just represent a small fraction (perhaps less than 5%) of the brain’s total activity, while the majority of its resources have been used on task-independent, spontaneous neural activity, and resting state fMRI (rs-fMRI) study is the best approach to evaluate it

[18]. Therefore, studies examining brain functional alterations during rest in MDD patients that carefully stratify groups by anhedonia will be a complement to current findings.

In this context, the aim of the present study was to investigate brain functional changes in patients with MDD that stratify groups by anhedonia using rs-fMRI. In the present study, a novel measure, voxel-mirrored homotopic connectivity (VMHC), also named homotopic resting-state functional connectivity (FC) was applied to process the rs-fMRI data [19]. VMHC measures the synchronicity of spontaneous functional activity between geometrically consistent mirrored regions of both hemispheres [20] and focuses more on the ability to incorporate information exchange and functional interactions between the two cerebral hemispheres [21]. Consequently, VMHC has been introduced to evaluate altered interhemispheric coordination in the study of a variety of psychiatric disorders, exploring the underlying pathophysiology [22, 23]. Based on previous evidence, we hypothesized that MDD with anhedonia would exhibit unique VMHC changes in certain brain regions and the altered regions might be distinct areas that could be applied to separate anhedonic MDD from non-anhedonic MDD.

Method

Participants

A total of 42 patients with MDD, including 22 MDD patients with anhedonia and 20 MDD patients without anhedonia, were recruited from Department of Psychiatry, The First Affiliated Hospital, Zhejiang University School of Medicine. For assignment to the MDD with anhedonia group, MDD patients must have been experiencing anhedonia according to the Item 2 (loss of interest or pleasure) of the symptom criteria (A) for MDD in the *Diagnostic and Statistical Manual of Mental Disorders, IV Edition (DSM-IV)* and the threshold of transformed score of Snaith-Hamilton Pleasure Scale (SHAPS) [24]. Each MDD patient met the DSM-IV diagnostic criteria for current unipolar MDD episode. The inclusion criteria for MDD patients also included: 1) aged 18–45 years; 2) drug-naïve patients with first-episode depression or recurrent depression with continued withdrawal of more than 3 months; 3) total score of the 17-item Hamilton Depression Scale (HAM-D-17) [25] ≥ 17 ; 4) right-handedness; 5) could follow the instructions to keep still during MRI scanning. Furthermore, twenty sex- and age-matched healthy controls (HCs) were recruited from local residents, hospital staffs, and students. The following exclusion criteria were applied to all subjects: 1) with a history of central nervous system diseases, such as epilepsy, serious head trauma, stroke or severe

mental retardation, medical conditions, or concomitant medications likely to affect the central nervous system; 2) alcohol or drug dependence or abuse; 3) female with pregnancy; 4) with a history of psychotherapy and physical therapy, such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and electroconvulsive therapy (ECT); 5) contraindications to MRI scan, including retractors or braces, metallic implants, and claustrophobia. Written informed consent was obtained and this study was approved by the local Ethic Committee of The First Affiliated Hospital, Zhejiang University School of Medicine.

Clinical assessment

The demographic and clinical data was collected by a self-designed questionnaire from all the participants. The Structured Clinical Interview for DSM-IV (SCID) was used for the diagnostic assessment of MDD and further psychiatric disorders, which was also administered to each subject. The severity of depression was evaluated by using HAM-D-17 [25]. Anhedonia was assessed by SHAPS [26]. This 14-item, reliable, and valid self-reporting questionnaire can yield four domains of hedonic experience, including interests and pastimes, social interactions, sensory experiences, and diet. Four answers to each item are possible: Strongly disagree, Disagree, Agree, or Strongly

agree. When the participant responses “Strongly agree” or “Agree”, the item is recorded a score of 0. In contrast, if the answer is “Disagree” or “Strongly disagree”, the score is 1. The total score of SHAPS represents the severity of anhedonia and the sum of transformed score > 5 indicates the presence of severe anhedonia [12]. The Chinese version of SHAPS was applied in our study, which had been demonstrated to be a useful and promising instrument in assessing anhedonia for clinical patients and non-clinical individuals in the Chinese settings [24]. The procedure performed in this study was shown in Fig. 1.

MRI acquisition

Imaging data were collected on a 3.0-T MRI scanner (Signa, HDxt, GE healthcare, USA), which is equipped with a standard birdcage head coil at the Magnetic Resonance Center of The First Affiliated Hospital, Zhejiang University School of Medicine. All subjects were asked to lie down with eyes closed and not to fall asleep. A brain volume (BRAVO) sequence was used for Sagittal 3D T1-weighted images with the following parameters: repetition time (TR)=7.3 ms, echo time (TE)=3.0 ms, flip angle=7°, field of view (FOV)=256 × 256 mm², Matrix=256 × 256, slice thickness=1 mm, slices=192. A gradient echo (GRE) and echo planar imaging (EPI) sequence was used to obtain rs-fMRI data with

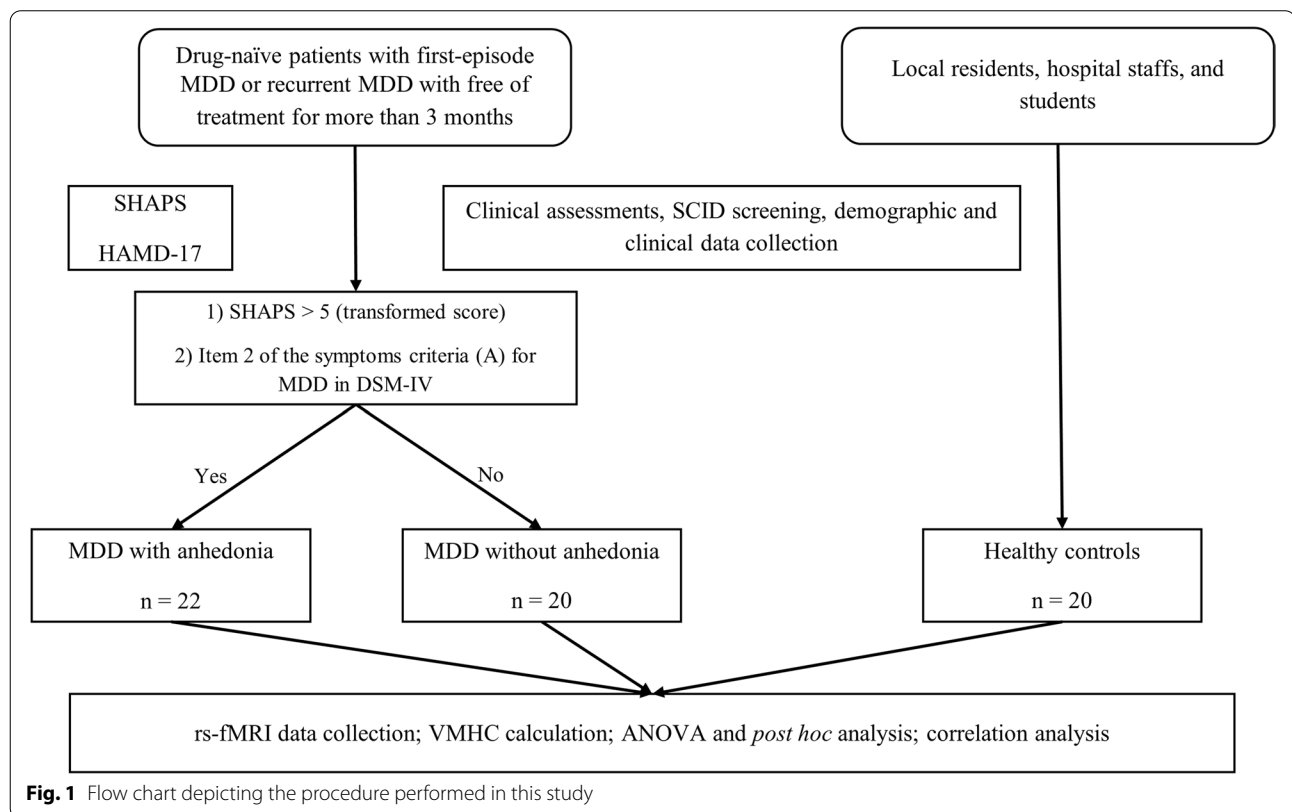


Fig. 1 Flow chart depicting the procedure performed in this study

the following parameters: axial slice, TR=2000 ms, TE=30 ms, flip angle=90°, FOV=220 × 220 mm², Matrix=64 × 64, slice thickness=4.0 mm, spacing=0.6 mm, slice order=interleaved and bottom-up, slices=33, measurements=180, scan time=6.00 min.

Data processing and VMHC analysis

All the rs-fMRI data were preprocessed by using Data Processing Assistant for Resting-State fMRI Advanced Edition V2.2 (DPARFSA, www.restfmri.net/forum/DPARFSA) [27] toolkit with Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>) in MATLAB (R2010b) (MathWork, Natick, MA, USA). The steps were as follows: 1) the first 10 images were excluded to ensure steady-state longitudinal magnetization was obtained; 2) slice timing was performed; 3) realignment for head motion correction was performed and any subjects with head motion > 3.0 mm translation or > 3.0° rotation in any direction were excluded; 4) the T1-weighted images were segmented into grey matter, white matter, and cerebrospinal fluid, and then the fMRI data were normalized to the standard Montreal Neurological Institute (MNI) space; 5) the normalized images were resampled to a voxel size of 3 × 3 × 3 mm³; 6) the generated images were smoothed with a Gaussian kernel having a full-width at half-maximum (FWHM) value of 4 mm; and 7) linear trend removal and temporal bandpass (0.01–0.1 Hz) filtering were finally conducted. For VMHC analysis, Pearson's correlations were computed between each time series and that of mirrored interhemispheric voxels. The correlation values were then transformed by Fisher's *z* to improve their normal distribution. The obtained VMHC maps were used for statistical analyses. Further details about data analysis can be found in previous studies [21, 28], such as the VMHC computation and generation of the standard symmetric brain template. The mean framewise displacement (FD) that indicated the temporal

derivative of the motion parameters was calculated by averaging *FD_i* from every time point for each subject [29]. In the present samples, the mean FD ranged from 0.03 to 0.16 mm.

Statistical analyses

The demographic and clinical data were analysed by using Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA). For categorical and continuous variables, the Chi-square tests (χ^2) and analyses of variance (ANOVAs) were used for statistical analyses respectively. The level of two-tailed statistical significance was set at $p < 0.05$ for all tests.

For VMHC comparisons, one-way ANOVA was calculated on the individual imaging maps in a voxel-by-voxel manner, and according to the results of ANOVA, a mask was built. Then, post hoc analyses, which based on the mask, were performed to identify the inter-group differences. Although age, sex, and educational level did not significantly differ among three groups, they were introduced as covariates in the measures. The results were corrected for multiple comparisons to a significant level of $p < 0.05$ by DPABI AlphaSim program with 10,000 iterations combining individual voxel threshold $p < 0.001$ with a minimum cluster size > 5 voxels for VMHC. Finally, the mean VMHC values of brain regions with significant group differences were extracted by using region of interest (ROI) analyses. The association analyses between VMHC values and clinical features in MDD patients were further performed.

Result

Demographic and clinical characteristics

Demographic and clinical features of MDD patients and HCs in the sample are summarized in Table 1. No significant difference was found in age, sex, and years of education among three groups of subjects (all $p > 0.05$). The two

Table 1 Demographic and clinical characteristics for all subjects ($n = 62$)

| | MDD with anhedonia, $n = 22$ means(SD) | MDD without anhedonia, $n = 20$ means(SD) | HCs, $n = 20$ means(SD) | Analysis F/χ^2 | p -values |
|---------------------------|---|--|----------------------------|---------------------|-------------|
| Age (years) | 28.6(7.73) | 29.1(7.70) | 27.7(5.07) | 0.223 | 0.801 |
| Gender (Male/Female) | 5/17 | 10/10 | 10/10 | 4.387 | 0.112 |
| Education years | 14.4(2.02) | 14.4(3.05) | 15.3(1.21) | 0.985 | 0.379 |
| Illness duration (months) | 23.4(27.5) | 19.9(22.9) | | 0.194 | 0.662 |
| Mean FD (mm) | 0.06(0.03) | 0.07(0.03) | 0.07(0.03) | 0.417 | 0.661 |
| SHAPS score | 37.7(7.09) | 26.7(3.76) | | 38.14 | 0.000 |
| HAMD score | 25.2(3.89) | 23.7(2.79) | | 2.097 | 0.155 |

HAMD Hamilton Depression Scale, HCs Healthy Controls MDD Major Depressive Disorder, FD framewise displacement, SD Standard Deviation, SHAPS Snaith-Hamilton Pleasure Scale

groups of MDD patients did not differ with respect to illness duration and scores of HAMD-17 (all $p > 0.05$). Specifically, MDD patients with anhedonia showed higher scores of SHAPS compared with MDD patients without anhedonia ($p < 0.05$).

VMHC differences among groups

The ANOVA revealed significant VMHC differences among three groups in the bilateral middle temporal

gyrus (MTG), superior frontal gyrus (SFG), and inferior parietal lobule (IPL) (Table 2 and Fig. 2). Relative to HCs, MDD with anhedonia showed significantly decreased VMHC in the bilateral MTG, as well as increased VMHC in the bilateral SFG (Table 3 and Fig. 3). Compared to MDD without anhedonia, MDD with anhedonia showed significantly decreased VMHC in the bilateral MTG and IPL, while increased VMHC in the bilateral SFG (Table 4 and Fig. 4). However, no

Table 2 Brain regions showing significant VMHC differences among MDD with and without anhedonia and HCs ($p < 0.05$, AlphaSim corrected)

| Brain region | Hemisphere | Cluster size | F value | MNI coordinate | | |
|--------------|------------|--------------|---------|----------------|-----|-----|
| | | | | x | y | z |
| MTG | L | 17 | 15.09 | -54 | 9 | -27 |
| | R | | | 54 | 9 | 27 |
| SFG | L | 20 | 13.84 | -12 | 57 | -21 |
| | R | | | 12 | 57 | -21 |
| IPL | L | 10 | 10.47 | -36 | -51 | 42 |
| | R | | | 36 | -51 | 42 |

HCs Healthy Controls, IPL Inferior Parietal Lobule, MTG Middle Temporal Gyrus, MDD Major Depressive Disorder, MNI Montreal Neurological Institute, SFG Superior Frontal Gyrus

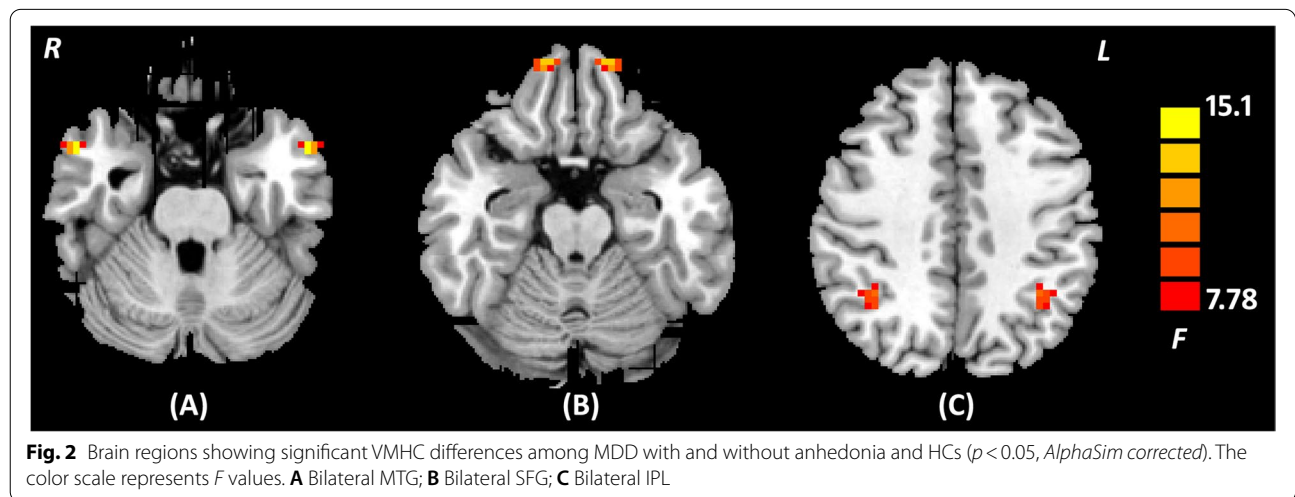


Table 3 Brain regions showing significant VMHC differences between MDD with anhedonia and HCs ($p < 0.05$, AlphaSim corrected)

| Brain region | Hemisphere | Cluster size | t value | MNI coordinate | | |
|--------------|------------|--------------|---------|----------------|----|-----|
| | | | | x | y | z |
| MTG | L | 17 | -5.368 | -54 | 6 | -27 |
| | R | | | 54 | 6 | -27 |
| SFG | L | 18 | 4.696 | -12 | 57 | -21 |
| | R | | | 12 | 57 | -21 |

HCs Healthy Controls, MTG Middle Temporal Gyrus, MDD Major Depressive Disorder, MNI Montreal Neurological Institute, SFG Superior Frontal Gyrus

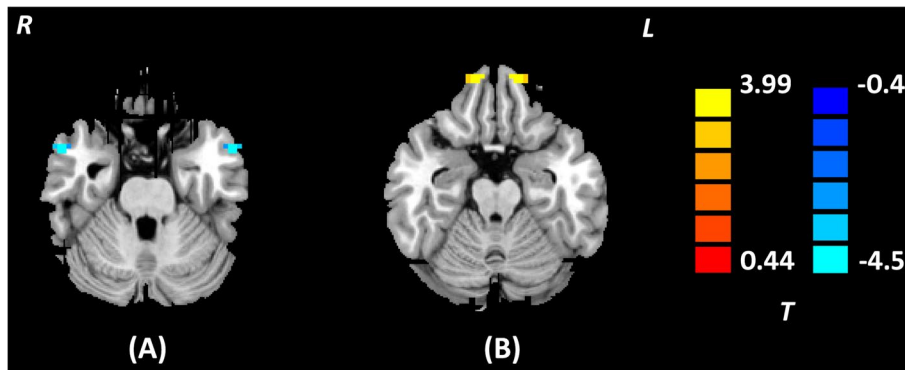


Fig. 3 Brain regions showing significant VMHC differences between MDD with anhedonia and HCs ($p < 0.05$, *AlphaSim* corrected). The color scale represents *t* values. **A** Bilateral MTG; **B** Bilateral SFG

Table 4 Brain regions showing significant VMHC differences between MDD with and without anhedonia ($p < 0.05$, *AlphaSim* corrected)

| Brain region | Hemisphere | Cluster size | t value | MNI coordinate | | |
|--------------|------------|--------------|---------|----------------|-----|-----|
| | | | | x | y | z |
| MTG | L | 8 | -4.330 | -57 | -6 | -21 |
| | R | | | 57 | -6 | -21 |
| SFG | L | 7 | 3.926 | -15 | 54 | -18 |
| | R | | | 15 | 54 | -18 |
| IPL | L | 10 | -5.629 | -36 | -48 | 42 |
| | R | | | 36 | -48 | 42 |

HCS Healthy Controls, IPL Inferior Parietal Lobule, MTG Middle Temporal Gyrus, MDD Major Depressive Disorder, MNI Montreal Neurological Institute, SFG Superior Frontal Gyrus

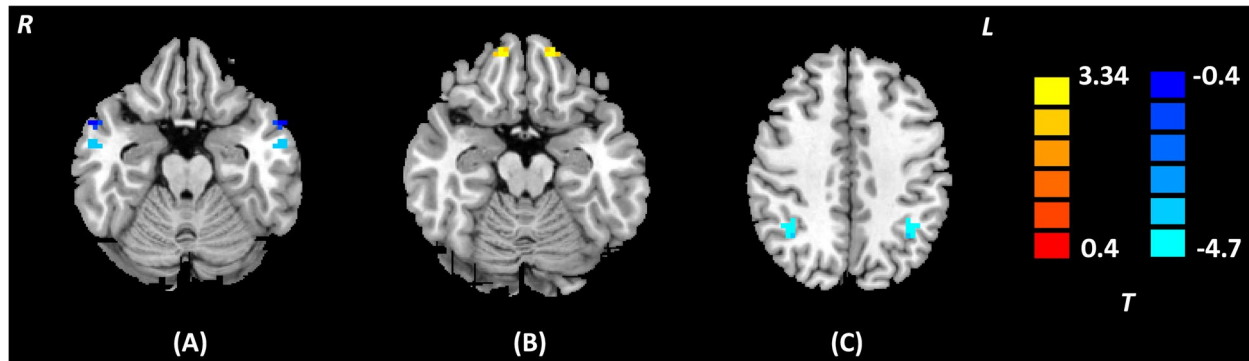


Fig. 4 Brain regions showing significant VMHC differences between MDD with and without anhedonia ($p < 0.05$, *AlphaSim* corrected). The color scale represents *t* values. **A** Bilateral MTG; **B** Bilateral SFG; **C** Bilateral IPL

significant difference was found between MDD without anhedonia and HCs. No significant associations were found between VMHC values of brain areas with group differences and clinical features in patients with MDD.

Discussion

In this study, the whole-brain interhemispheric connectivity as measured by VHMC in MDD patients with respect to anhedonia was examined. Our results revealed that MDD patients without anhedonia was less likely to

be associated with aberrant interhemispheric connectivity, but current MDD diagnosis and anhedonia combined seemed to be good predictors of altered VMHC in the SFG, MTG, and IPL. Our present findings demonstrated that MDD patients with and without anhedonia exhibited different patterns of intrinsic brain features and together with prior evidence [30], the current findings might also suggest that MDD with anhedonia could be treated as a functional subtype of depression with unique neuroimaging underpinnings. MDD is a heterogeneous disorder varying considerably in clinical manifestation, progression, treatment response and neurobiology [31]. The huge heterogeneity of MDD, especially in biological terms, presents a major obstacle for the development of new drugs and precision medicine [30]. Our findings provide insight into MDD heterogeneity in biological and clinical aspects and may represent a promising step toward the development of personalized management for MDD.

Importantly, the present study observed increased VMHC values in the SFG in MDD patients with anhedonia. Functional deficits in many regions of the prefrontal cortex (PFC) have been implicated in anhedonia [32]. It is well acknowledged that the SFG locates at the superior part of the PFC and is generally considered as a key brain area in emotion regulation-related processes [33]. Previous studies have already observed a relationship between the SFG dysfunction and anhedonia development. It has been found that disrupted cerebral functional nodal characteristics of the SFG, measured by efficiency and degree, are associated with the severity of anhedonia in patients with MDD [34]. Consummatory anhedonia was found to be correlated with abnormal FC of the SFG to subregions of the anterior cingulate cortex (ACC) in a group of MDD patients [35]. Interestingly, increased SFG connectivity with the left ventral caudate over time was associated with anhedonia improvement in a prior report [36]. Furthermore, task-related fMRI studies also reported that abnormal activation across frontal regions during reward processing tasks correlated with anhedonia in MDD [37]. Together with our current discovering, all these findings may be emphasizing the crucial role of the SFG in regulating the experience of pleasure.

In the present study, MDD patients with anhedonia exhibited decreased VMHC values in the MTG. The temporal cortex has been illustrated to be involved in emotion regulation, attention control, memory processing, and social cognition [38–42], in which the MTG participated in cued attention [43]. A previous study reported that melancholic MDD showed decreased network homogeneity (NH) in the right MTG relative to HCs [44], thus, dysfunction in the MTG might be associated with anhedonia since one of the distinctive clinical presentations of melancholic MDD was anhedonia [45].

In a recent study, increased anhedonia severity was found to be correlated with the magnitude of ventral caudate FC with the cuneus and the MTG in patients with first-episode drug-naïve MDD, suggesting that the temporal area participated in reward-related behavior as well [46]. Meanwhile, the MTG is involved in the default mode network (DMN), and abnormal functional alterations of the DMN might be characteristic of anhedonia [47]. A study investigating the neural correlates of posttraumatic anhedonia symptoms demonstrated that decreased FC between the brain DMN regions specifically correlated to anhedonia symptoms [48]. In addition, impaired reward responsivity, a representation of anhedonia symptom, was associated with DMN hyperconnectivity [49] and reductions in FC within the DMN co-occurred with anhedonia improvement across two psychosocial treatments for anhedonia [50]. In view of the above-mentioned facts, we speculated that aberrant interhemispheric FC of the MTG was critical to the neurobiology of anhedonia.

Decreased VMHC values in the IPL was also found in MDD patients with anhedonia when comparing to MDD without anhedonia. The IPL, a part of the frontoparietal network, has a key role in directly representing associations between tasks and rewards, alongside directly linking cognitive control and motivational functions in the brain [51]. In a prior case report, a 71-year-old right-handed man developed an infarction in the right IPL which was associated with musical anhedonia subsequently, namely selective impairment of emotional experience in listening to music [52], suggesting the potential role of the IPL in anhedonia. In the meantime, a positive correlation was indicated between levels of social anhedonia and the thickness of the inferior parietal gyri in a non-clinical sample, which contributed to the understanding of the importance of IPL in anhedonia development [53]. Although not correlated with anhedonia severity, a very large bilateral, but right-dominant, fronto-temporo-parietal network was activated during an unexpected reward gain task in a group of patients with psychiatric symptoms, exhibiting a full range of anhedonia [54]. Consistently, our novel results added to the literature on involvement of the frontal–temporal-parietal circuit dysfunction in MDD patients with anhedonia.

Certain limitations of our study should be mentioned. First, our sample size was relatively small, thus, the current findings should be understood as preliminary and tentative, which required to be verified in larger cohorts of MDD patients with anhedonia. Second, previous studies have found that different types of anhedonia may have specific impacts on neural function [14], however, due to the modest sample size, we did not investigate the effects of different types of anhedonia on brain functional alterations.

Third, this study was a cross-sectional design, the causal relationship of altered brain function with anhedonia in MDD could not be directly determined.

Conclusion

In conclusion, the present findings suggest that MDD with and without anhedonia exhibit different patterns of inter-hemispheric connectivity. Anhedonia in MDD is related to aberrant interhemispheric connectivity within brain regions involved in the frontal–temporal-parietal circuit.

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Authors' contributions

Authors Shaojia Lu, Jiamin Shao, and Qian Feng: conducted the statistical analyses and wrote the first draft of the manuscript. Authors Lili Jia and Zheng Wang: finished the clinical assessments. Authors Congchong Wu, Shaohua Hu and Yi Xu: recruited the sample and revised the manuscript. Authors Manli Huang and Yi Xu: designed the study and had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to and have approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethic committee of The First Affiliated Hospital, Zhejiang University School of Medicine. All subjects provided written informed consent prior to participation. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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