

Neuroimaging in psychiatry mood disorders 2023

Edited by

Serdar M. Dursun and Massimo Tusconi

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Neuroimaging in psychiatry 2023: mood disorders

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Editorial: Neuroimaging in psychiatry 2023: mood disorders

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neuroimaging, biomarkers, neurobiology, mood, bipolar disorder, Bd

Editorial on the Research Topic

Neuroimaging in psychiatry 2023: mood disorders

The field of neuroimaging has made significant progress in recent decades, significantly influencing the understanding and treatment of psychiatric disorders, particularly mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD) (1–4). These complex conditions, characterized by pervasive mood, affect, and behavioral symptoms, have long been a challenge for diagnosis and treatment because of their multifactorial etiology and the absence of definitive biomarkers (5). The role of neuroimaging in psychiatry has expanded beyond traditional structural imaging techniques to encompass a variety of advanced modalities, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS) (6–8). These techniques have facilitated a more nuanced understanding of the neural circuits implicated in mood disorders, elucidating abnormalities in brain regions such as the prefrontal cortex, amygdala, hippocampus, and anterior cingulate cortex (9). Neuroimaging has emerged as a crucial tool for unraveling the neurobiological underpinnings of these disorders, providing insights that are beginning to bridge the gap between clinical symptomatology and the basis of the disorders (10–14). Functional studies on Major Depressive Disorder have identified hypoactivation in the dorsolateral prefrontal cortex (DLPFC) during tasks requiring executive function and cognitive control, as well as hyperactivation of the amygdala in response to negative emotional stimuli (15). These findings have been interpreted as reflecting a dysregulated neural circuit, wherein diminished top-down control from the prefrontal cortex fails to modulate hyperactive limbic structures, leading to the emotional and cognitive disturbances characteristic of depression (16–20). Studies on MDD have documented structural abnormalities such as reduced gray matter volume in the prefrontal cortex and temporal lobes, as well as functional alterations in the ventral prefrontal cortex and striatum (21, 22). Bipolar disorder, with its alternating episodes of mania and depression, presents a more complex neuroimaging profile (12, 23). The Research Topic brings together a diverse array of manuscripts that utilize neuroimaging to explore structural and functional alterations in mood disorders. A central theme emerging across the contributions is the identification of potential neurobiological biomarkers through advanced imaging techniques, with a particular focus on distinguishing features of MDD and BD (24–27). The Research Topic describes multiple aspects of neuroimaging, in

particular diagnostic groups (MDD vs. BD), neuroimaging techniques (fMRI, EEG), and insights into targeted brain areas.

In the context of diagnostic stratification, Schreiber et al. identified a significant enlargement of the left vagus nerve cross-sectional area (VN-CSA) in individuals with Major Depressive Disorder (MDD), particularly among those with recurrent episodes. This morphological alteration of the cervical vagus nerve may serve as a novel imaging biomarker, offering potential insights into the somatic underpinnings of depressive pathology.

Additionally, Estudillo-Guerra et al. revealed in their study a trend indicating a higher perfusion imbalance in the left superior and middle frontal gyrus during mania and the right superior and middle frontal gyrus during euthymia phases in participants with Bipolar Disorder Type I.

In the topic concerning neuroimaging techniques (fMRI, EEG), Huang et al. compared functional and structural MRI abnormalities between bipolar and unipolar depression. They found that the BD group exhibited an increased fractional amplitude of low-frequency fluctuation (fALFF) in the hippocampus compared with both the healthy control (HC) and MDD groups.

Furthermore, Liu et al. proposed a multi-scale spatial-temporal local sequential and global parallel convolutional model. This method aimed to improve the diagnostic accuracy of Generalized Anxiety Disorder, particularly in the context of mood instability, using high-frequency electroencephalogram (EEG) signals.

In their investigation of Major Depressive Disorder (MDD) using functional magnetic resonance imaging (fMRI), Endo et al. identified specific dynamic brain activity patterns, referred to as dynamic modes, that occurred with either increased or decreased frequency in individuals with MDD compared to healthy controls. These alterations suggest a disruption in the temporal organization of neural networks, potentially reflecting impaired flexibility and adaptability in brain function (28–30). Such findings contribute to the growing body of evidence supporting the role of dynamic functional connectivity as a potential state-sensitive biomarker in mood disorders.

To complement the theme, Willinger et al. reported weakened effective connectivity between the salience network and the default mode network during the resting state in participants with adolescent depression. They suggested that this pattern may reflect a hierarchical imbalance between the default mode network (DMN) and the salience network (SN).

Chen et al. using a machine learning approach, examined abnormal voxel-mirrored homotopic connectivity in participants with first-episode MDD. They found reduced functional connectivity in the bilateral middle frontal gyrus, fusiform gyrus, medial superior frontal gyrus, and precentral gyrus. These alterations may be linked to depressive symptoms and could serve as a potential biomarker of MDD.

Delving deeper into the discussion regarding the morphobiological aspects of targeted brain areas, Liu et al. observed altered functional activity in the right fusiform gyrus and the left superior temporal gyrus in individuals with treatment-resistant depression following a dual-target accelerated transcranial magnetic stimulation protocol.

Examining structural alterations in participants with MDD, Wang et al. reported a region-specific reduction in cortical thickness, particularly within the left rostral middle frontal gyrus. This thinning exhibited a significant negative correlation with illness duration, suggesting a progressive neuroanatomical deterioration associated with the chronicity of depressive episodes. These findings underscore the potential of cortical metrics, such as reductions in the rostral middle frontal gyrus, as longitudinal markers of disease burden and progression in MDD.

Kijima et al. explored how fronto-striato network function is reduced in participants with MDD highlighting that the reward system network may be an important biological marker of MDD, although careful consideration should be given to age and its association with the severity of the disorder.

Finally, Cong et al. examined hippocampal subfield morphology in participants with first-episode BD type II and major depressive disorder within a drug-naïve Chinese cohort. They reported a significant increase in hippocampal volume, particularly on the left side, observed only in the MDD group compared with healthy controls, and not in the BD-II group. This finding was specific to the studied sample and requires replication in larger, independent cohorts to confirm its validity.

Across the included studies, several key themes emerge, including the potential of specific brain regions (DLPFC, hippocampus) and connectivity patterns (DMN-SN interaction) as diagnostic and therapeutic biomarkers, the utility of machine learning in neuroimaging classification tasks, and the convergence of structural and functional findings in delineating mood disorder subtypes. In conclusion, the most recent advances in neuroimaging technology over the past two decades have greatly deepened our understanding of the neurobiological basis of mood disorders (31–34). By revealing the structural and functional abnormalities associated with MDD and BD, these tools have not only improved diagnostic accuracy but also opened new avenues for the creation of personalized medicine strategies. The integration of neuroimaging with other emerging fields, such as genomics, epigenetics, and machine learning, promises a more nuanced approach to psychiatry, in which treatment can be tailored to the individual's unique neural and genetic profile. By continuing to harness the power of neuroimaging, the convergence of technology and neuroscience holds promise for the development of more effective and personalized treatments for mood disorders, with the potential to significantly improve clinical outcomes. While the findings discussed in this Research Topic offer promising directions, it is essential to emphasize that many of the identified alterations should be considered potential biomarkers. Further validation in larger, longitudinal, and translational studies is warranted to ascertain their clinical applicability and reliability. Such scientific prudence remains vital to advancing the field responsibly.

Author contributions

MT: Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing. SD:

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Conflict of interest

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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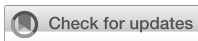
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Enlarged cross-sectional area of the left vagus nerve in patients with major depressive disorder

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Purpose: Autonomic dysfunction and a chronic low-grade inflammation are supposed to play a role in the etiology of major depressive disorder (MDD). The vagus nerves (VN) form a major part of the parasympathetic nervous system and of the gut-brain axis. They are supposed to exert anti-inflammatory and epithelial barrier protective effects in the gut. A reduced vagal activity was described in patients with MDD. We aimed to examine the VN in patients with MDD with high-resolution ultrasound (HRUS) and hypothesized that the cross-sectional area (CSA) and the echogenicity of the VNs were altered in comparison to healthy controls.

Materials and methods: The echogenicity (gray scale mean) and the CSA of the cervical VNs at the level of the thyroid gland and both median nerves were examined with HRUS in 50 patients with MDD and 50 matched healthy controls.

Results: The left VN-CSA was significantly larger in the MDD group compared to the control group ($1.7 \pm 0.4 \text{ mm}^2$ versus $1.5 \pm 0.4 \text{ mm}^2$; $p = 0.045$). The CSA of the right VN and both median nerves (MN) were similar between groups. In MDD subgroup analyses, recurrent depressive disorders were the main contributing factor for the left VN-CSA enlargement. Echogenicity was not altered in the VN and MN between groups.

Conclusion: The enlargement of the left VN-CSA in patients with MDD, and especially in these patients with recurrent depressive disorders, might turn out as a promising imaging biomarker. Longitudinal studies are warranted to examine whether the VNs-CSA change in the course of MDD.

KEYWORDS

major depressive disorder, vagus nerve, ultrasound, autonomic nervous system, gut-brain axis, inflammation, depression

Introduction

As the vagus nerves (VNs) are of particular importance in psychiatric and neurological disorders, sonographic research has witnessed a growing interest (1–3). The VNs constitute a crucial part of the parasympathetic autonomic nervous system (ANS). The functional imbalance between reduced VN activity and the sympathetic system results in autonomic dysfunction, comprising symptoms like palpitations, impairment of sleep, appetite, and gastrointestinal functioning in neuropsychiatric disorders, e.g., major depressive disorder (MDD) (4). Currently, antidepressant treatments, such as vagus nerve stimulation (VNS), where the left VN is used as a target for electrical stimulation,

emerged as an option in treatment-resistant depression (5). Meta-analyses also demonstrated a negative association between vagal activity and inflammatory markers (6). A lack of vagal inhibition of systemic inflammatory processes seems to play a key role in the low-grade inflammation pathogenesis approach of MDD (7). Moreover, the VNs form a central part of the gut-brain axis by linking the gut and abdominal organs with the central nervous system, thus, enabling a bidirectional communication (8). Disturbances of the microbiota and the gut-brain axis are also supposed to contribute to the etiology of depression and anxiety disorders (8, 9).

High-resolution ultrasound (HRUS) allows the reliable examinations of the VNs *in vivo* (10). Previous findings showed that sonomorphological VN alterations and autonomic function may correlate in healthy probands (11). Morphological alterations of the cervical VNs were described in different neurological disorders. An atrophy was found in patients with Parkinson's Disease (PD) [e.g., (1, 12)], while an enlargement of the VN-CSA was associated with autonomic dysfunction in patients with Guillain-Barré-Strohl syndrome (13).

So far, although there is cumulating evidence for a relevant role of the VNs in the etiology of MDD, there are no morphological examinations of the VNs in these patients *in vivo*. Thus, we aimed to examine the VNs in patients with MDD with HRUS and hypothesized that the CSA and the echogenicity of the VNs were altered in comparison to healthy controls.

Materials and methods

This study was performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendment. It was approved by the local Ethics Committee of the Medical Faculty at the University of Leipzig (reference number 425/19-ek). All participants gave informed and written consent for participation in medical research.

Based on studies that examined the size of the VNs in predominantly neurodegenerative disorders where the differences in the CSA of the asymmetric VNs varied between 10% (in case of the right VN) and 20% (in case of the left VN) (1), we calculated that, using a two-tailed test, 53 patients with MDD had to be examined to detect a difference in the CSA of 15% with a power of 0.8. The entire cohort comprised 100 adult subjects (50 patients with MDD and 50 healthy controls) and was balanced according to sex and age (Table 1). Participants were recruited from 06/2020 to 09/2021 from the inpatient ward of the Department of Psychiatry and Psychotherapy, University of Leipzig Medical Center.

All patients had to fulfill the clinical criteria of depression (F32.1–F32.2 and F33.1–F33.3) as defined by the International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Diagnoses were confirmed during the treatment by psychiatric consultants.

Exclusion criteria were a medical history of polyneuropathy, epilepsy, neurodegenerative disorders, use of illegal substances, any addictive diseases, any psychiatric diagnoses in the control group, organic or psychotic psychiatric comorbidities, any relevant anxiety and / or obsessive compulsive disorders in the MDD group, a history of head injury, or acute somatic diagnoses during the time of

examination. All participants underwent a profound neurological examination to exclude persons with clinically apparent yet hitherto unknown polyneuropathy or parkinsonism.

At the time point of study participation, all patients in the MDD group were on antidepressants and had psychotherapy. We did not assess how long and how often patients had psychotherapy before their participation in this study nor which kind of psychotherapy they had in before. We also did not assess the history of antidepressant intake before study participation.

To evaluate the severity of depression at the time of participation, all participants completed the Beck Depression Inventory (BDI) and Patient Health Questionnaire-15 (PHQ-15) with focus on somatic symptoms.

The HRUS examination was performed with an Aplio i800 (Canon Medical Systems, Neuss, Germany) with a 24MHz linear transducer. Briefly, both VNs, at the level of the thyroid gland, and, for control purpose, both median nerves (MN), 10 cm proximal to the wrist, were examined according to established protocols (10, 14) (Figure 1). Three B-mode images of each nerve and side were recorded and optimized regarding brightness, depth, and focus. The identified nerve was marked roughly with the marking tool of the ultrasound device, and the images were stored for *offline* measurement of the CSA. Post-examination *offline* measurements were performed with ImageJ (National Institutes of Health, Bethesda, Maryland, United States; version 1.53a). The CSA was determined with a precision of 0.1 mm². Further statistics were calculated with the median of the 3 CSA values of each nerve and side, which is less likely to be distorted by outliers.

In order to determine the echogenicity of the nerves, the image with the median CSA was converted into an 8-bit black and white image in which each pixel is assigned a grayscale. The grayscales ranged from 0 (black) to 255 (white). An average value of the grayscales of all pixels within the CSA was calculated (grayscale mean, GSM). To determine the echogenicity independently of brightness settings of the ultrasound device, the GSM of the VN was set in relation to the GSM of the blood in the ipsilateral common carotid artery (CCA), which is physiologically hypoechoic and shows little heterogeneity. The GSM ratio (GSM-VN / GSM-CCA) was used for further statistics.

All measurements were done by the same rater who was blinded to the side of the nerve (left vs. right) and to group affiliation (control vs. MDD).

Statistical analyses were performed by using IBM SPSS Statistics (IBM Corporation, Armonk, New York, United States; version 27.0). To assess intra-rater agreement 20 images were re-measured (ICC-coefficient = 0.996, $p < 0.001$). CSA values of one rater were used for statistical analyses. For group comparison, the student's *t*-test (for data with normal distribution) and Mann–Whitney *U*-test (for non-normal distribution) were used. Chi-square test was applied on group comparisons of nominally scaled data. Correlation coefficients were calculated using Pearson's correlation (normal distribution, metric level), Spearman's correlation (non-normal distribution, ordinal level) and Eta Coefficient (nominal and metric level). The subgroup analysis was performed using Kruskal–Wallis one-way ANOVA. Extreme outliers were excluded based on Tukey's hinges (first quartile $-3 \times$ interquartile range (IQR) and third quartile $+3 \times$ IQR), visualized in boxplots (15). The significance level was set at $p < 0.05$.

TABLE 1 Demographic data of patients with major depressive disorder (MDD) and healthy controls.

Characteristics	MDD group (n = 50)	Control group (n = 50)	p-value
Male (n)	21	21	1.00°
Female (n)	29	29	1.00°
Age in years (mean, ± SD, range)	45 ± 16 (21–80)	46 ± 21 (22–80)	0.972#
Height in cm (mean, ± SD, range)	172 ± 10 (146–20)	173 ± 10 (153–192)	0.890+
BMI (kg/m²; mean, ± SD, range)	26.6 ± 5.7 (17.1–46.9)	24.5 ± 3.6 (19.5–38.0)	0.049#
Medical history of comorbidities			
Cardiac arrhythmia [n (%)]	5 (10%)	1 (2%)	0.092°
Diabetes mellitus [n (%)]	3 (6%)	1 (2%)	0.307°
Questionnaires			
BDI score (median, range)	24.5 (6–46)	4 (0–20)	0.001#
PHQ-15 score (median, range)	13 (1–22)	4 (0–20)	0.001#
Duration of actual depressive episode in weeks (mean, SD, range)	25.39 ± 18.74*	0	
	4–80*		

+Student's *t*-test; #Mann–Whitney *U*-test; °Chi-square test; BMI, body mass index; BDI, Beck Depression Inventory; PHQ-15, Patient Health Questionnaire-15; SD, standard deviation. *One extreme outlier of 400 weeks duration was excluded.

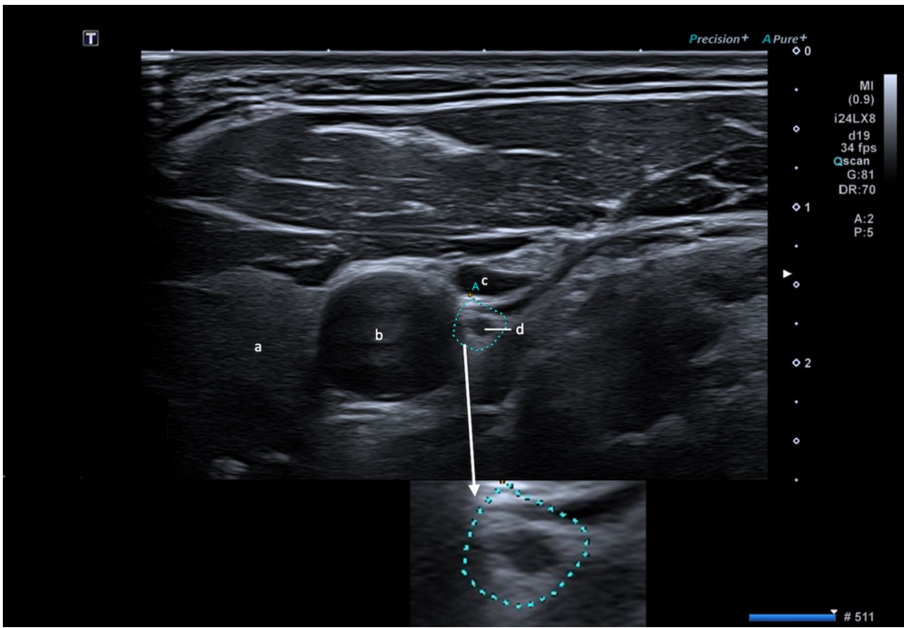


FIGURE 1 Visualization of the vagus nerve (d) with embedded magnification. a: thyroid gland; b: common carotid artery; c: internal jugular vein; scale bar = 1 cm.

Results

Demographic data of patients with MDD and the control group were well-balanced in terms of sex, age, and height. Only the BMI was significantly higher in the MDD group. No significant differences for known cardiac arrhythmia or diabetes mellitus in the medical history were found between both groups. BDI and PHQ-15 scores were significantly higher in the MDD group. In the MDD group, the current depressive episode persisted at the time of examination for a mean of 25 weeks (after exclusion of one extreme outlier of 400 weeks; Table 1).

In HRUS examinations, the left VN-CSA was significantly larger in the MDD group than in the control group ($p = 0.045$), while the right VN-CSA did not differ significantly between groups (Table 2). In the MDD group, no significant correlations were found between the duration of the depressive episode and the left VN-CSA ($p = -0.12$; $p = 0.413$) or right VN-CSA ($p = 0.04$; $p = 0.785$), the BDI score and the left VN-CSA ($p = -0.184$; $p = 0.201$) or the right VN-CSA ($p = 0.009$; $p = 0.952$), nor the PHQ-15 score and the left VN-CSA ($p = -0.134$; $p = 0.353$) or the right VN-CSA ($p = 0.031$; $p = 0.833$). The left and right MN-CSA were similar between the control group and the MDD group (Table 2).

TABLE 2 High-resolution ultrasound data of patients with major depressive disorders (MDD) and healthy controls.

Variable		MDD group	Control group	<i>p</i> -value
VN-CSA left (mm ²)	Mean, SD	1.7 ± 0.4	1.5 ± 0.4	0.045 ⁺
VN-CSA right (mm ²)	Mean, SD	1.8 ± 0.5	1.7 ± 0.5	0.269 ⁺
MN-CSA left (mm ²)	Mean, SD	6.9 ± 1.3	6.5 ± 1.2	0.079 ⁺
MN-CSA right (mm ²)	Mean, SD	6.8 ± 1.3	6.5 ± 1.2	0.063 ⁺
VN GSM-Index left	Mean, SD	4.5 ± 2.4	5.3 ± 4.6	0.482 [#]
VN GSM-Index right	Mean, SD	5.3 ± 4.7	6.1 ± 5.9	0.328 [#]

⁺Student's *t*-test; [#]Mann–Whitney *U*-test; HRUS, high-resolution ultrasound; VN, vagus nerve; CSA, cross-sectional area; GSM, gray scale mean; SD, standard deviation.

TABLE 3 Demographic and high-resolution ultrasound data of subgroups of patients with major depressive disorder.

Characteristics	FD group (<i>n</i> = 18)	RDD group (<i>n</i> = 32)
Male (<i>n</i>)	7	14
Female (<i>n</i>)	11	18
Age in years (mean, ± SD, range)	39 ± 15 (22–64)	49 ± 17 (21–80)
Height in cm (mean, ± SD, range)	173 ± 11 (158–200)	172 ± 9 (146–191)
BMI (kg/m ² ; mean, ± SD, range)	24.2 ± 4.4 (17.1–31.8)	27.9 ± 5.9 (20.1–46.9)
Questionnaires		
BDI score (median, range)	27.5 (6–44)	23 (8–46)
PHQ-15 score (median, range)	13 (1–22)	12.5 (1–21)
Duration of actual depressive episode in weeks (mean, ± SD)	28.8 ± 21.2*	23.6 ± 17.4
Ultrasound examination		
VN-CSA left (mm ² ; mean, ± SD)	1.6 ± 0.4	1.7 ± 0.4
VN-CSA right (mm ² ; mean, ± SD)	1.9 ± 0.5	1.8 ± 0.5
MN-CSA left (mm ² ; mean, ± SD)	7.0 ± 1.6	6.9 ± 1.2
MN-CSA right (mm ² ; mean, ± SD)	6.9 ± 1.6	6.7 ± 1.2
VN GSM-Index left (mean, ± SD)	4.3 ± 2.4	4.6 ± 2.4
VN GSM-Index right (mean, ± SD)	5.7 ± 3.1	5.1 ± 5.4

FD, first time diagnosis; RDD, recurrent depressive disorder; SD, standard deviation; BDI, Beck Depression Inventory; PHQ-15, Patient Health Questionnaire-15; MN, median nerve; VN, vagus nerve; CSA, cross-sectional area; GSM, gray scale mean. *One extreme outlier of 400 weeks duration was excluded.

TABLE 4 Subgroup analysis with Kruskal–Wallis one-way ANOVA between major depressive disorder patients with first time diagnosis (FD), recurrent depressive disorder (RDD), and control group for left and right vagus nerve (VN) cross-sectional area (CSA).

	Left VN-CSA	Right VN-CSA
	Adapted <i>p</i> -value	Adapted <i>p</i> -value
Control group/RDD	0.03	1.00
Control group/FD	1.00	0.683
FD/RDD	0.386	1.00

The MDD group was further stratified into two subgroups: first time diagnosis (FD; *N* = 18) and recurrent depressive disorder (RDD; *N* = 32; Table 3). Kruskal–Wallis one-way ANOVA revealed that the RDD subgroup contributed mainly to the significant enlargement of the left VN-CSA in comparison to the control group (*p* = 0.03; Table 4). For the right VN-CSA, Kruskal–Wallis one-way ANOVA showed no significant differences between MDD subgroups and the control group (Table 4).

TABLE 5 Subgroup analysis with Kruskal–Wallis one-way ANOVA between major depressive disorder patients with first time diagnosis (FD), recurrent depressive disorder (RDD), and control group for left and right vagus nerve (VN) gray scale mean (GSM) index.

	Left VN-GSM-index	Right VN-GSM-index
	Adapted <i>p</i> -value	Adapted <i>p</i> -value
Control group/RDD	1.00	0.279
Control group/FD	1.00	1.00
FD/RDD	1.00	0.247

Regarding the echogenicity of the VNs, no significant differences were found between the control and the MDD group (Table 2), or its subgroups (Table 5). In both control and MDD group, a higher GSM-Index was measured for the right VN in comparison to the left VN (Mann–Whitney *U*-test *p* < 0.001; Table 2). In the MDD group, no significant correlation was found neither between the BDI score and the left (*p* = 0.143; *p* = 0.320) or the right GSM-Index (*p* = 0.201;

$p = 0.161$), nor between PHQ-15 score and the left ($p = -0.174$; $p = 0.277$) or the right GSM-Index ($p = 0.190$; $p = 0.186$). In the whole study cohort, the right VN-CSA correlated significantly with the right GSM-Index ($p = 0.227$; $p = 0.023$), whereas the left VN-CSA and the left GSM-Index showed no significant correlation ($p = -0.057$; $p = 0.571$).

Sex, age, BMI, height, cardiac arrhythmia, and diabetes mellitus were not identified as covariates for the VN-CSA nor for the VN echogenicity.

Discussion

For the first time, this study revealed morphological changes of the cervical VNs in patients with MDD. The left VN-CSA was significantly enlarged in comparison to healthy subjects. Noteworthy, this enlargement of the left VN-CSA in patients with MDD was mainly driven by the subgroup of patients with recurrent depressive disorder.

Over the last decade, HRUS enabled the reliable examination of small nerves like the VN (10). A reduced VN-CSA was repeatedly measured in neurodegenerative disorders like PD or amyotrophic lateral sclerosis (1, 2, 12), while enlarged VN-CSA was described in inflammatory (13, 16, 17), but also in hereditary neuropathies (18). The enlarged left VN-CSA in patients with MDD and especially in the subgroup of patients with RDD might be due to a subtle inflammatory edema of the left VN. Other explanations like hereditary or inflammatory polyneuropathies (18) are unlikely because of the unaffected MNs, and participants with clinical signs of a polyneuropathy in the profound neurological examination were excluded from this study. Compression of nerves can also cause enlarged CSAs, however, during the HRUS examination the VN was visualized over its cervical course and no compression or entrapment was noted. Thus, the most probable explanation for the small (about 10%) but significant difference in the CSAs of the left VN remains a (chronic) inflammation which leads to an edema with subsequent VN enlargement. The VNs were also found to be enlarged in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (17, 19). Interestingly, patients with CIDP may also show a subtle affection of the ANS with focus on parasympathetic cardiovascular fibers (20), and they may suffer from neuropsychiatric symptoms and disorders like pain, fatigue, and depression (21, 22). However, so far depressive symptoms in patients with inflammatory polyneuropathies are thought to be reactive due to the patients' functional impairment and not to be related to the inflammation of the peripheral nervous system or the VN (21).

The VNs with their afferent and efferent fibers also play a crucial role in connecting the gut and the brain. Recently, cumulate research suggested that a disturbance of the microbiota and the gut-brain axis might contribute to the etiology of depression (8, 9). In their review, Tan and colleagues argued that the immune response to gut microbiota translocation induced by a leaky gut may be responsible for the chronic inflammatory condition in depression. Pro-inflammatory cytokines like IL-2, IL-12, or TNF- α were repeatedly shown to be over-expressed in patients with MDD which

points to a role of inflammation in the pathophysiology of MDD (23–28). The TNF- α inhibitor etanercept was effective in treatment-resistant depression and reduced depression and anxiety in psoriasis patients (29, 30). Consequently, modulating inflammation and immune regulation in patients with MDD emerged as a potential drug target (31).

Furthermore, the VNs may exert anti-inflammatory and epithelial barrier protective effects in the gut (8). The interactions between the immune system and the central nervous system are characterized by a bidirectional communication that aims to specify the immune defense of the host (32). Physiologically, the afferents of the VNs can sense a peripheral infection and transmit this information to the central nervous system which is shielded from the rest of the body by the blood brain barrier (32). This information may then be redirected to vagal efferents which can send anti-inflammatory responses through the inhibition of pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-1, and the release of anti-inflammatory cytokines such as IL-10 (7, 33). This is also referred to as the “inflammatory reflex” of the VN (7, 33, 34). Thus, an (ongoing) inflammation of the VNs could restrict vagal activity and might lead to a lack of vagal downregulation of inflammatory processes. A reduced vagal activity was repeatedly described in patients with MDD (35, 36), and was mitigated after the onset of antidepressant treatment (36). The MDD subgroup analysis showed that the enlargement of the left VN-CSA was mainly driven by the RDD subgroup. We assume, that recurrent depressive episodes might trigger a chronification of vagal dysfunction by oversteering the anti-inflammatory functions of the VNs in the long term (37).

Considering side-specific effects of the VNs, in healthy subjects, Pelz et al. found an *inverse* correlation only between the left VN-CSA and parameters of parasympathetic activity (11). Left VN efferent neurons were also prominently involved in anti-inflammatory effects, at least in mice, where the selective stimulation of efferent cholinergic VN neurons originating in the left dorsal motor nucleus and projecting to the celiac-superior mesenteric ganglia significantly increased splenic nerve activity and inhibited TNF- α production (38). The so-called cholinergic anti-inflammatory pathway is exerted through vago-parasympathetic reflexes via the splenic nerve and vagal efferent neurons to enteric neurons resulting in a decrease of TNF- α (33). In humans, invasive VNS was approved for severe treatment-resistant depression in 2005 by the US Food and Drug Administration. Usually, the left cervical VN is stimulated (5, 39). Recently, left VNS also emerged as a promising treatment approach for inflammatory bowel disease (40, 41).

So far, echogenicity of nerves was examined only in a few studies. Gamber and colleagues did not find a general difference in the nerves' echogenicity between patients with CIDP and probands, but differences between the subgroups of clinically progressive CIDP patients compared to healthy controls and stable CIDP patients (42). No differences were found in the echogenicity of the VNs between MDD and controls. One explanation may be, that the epineurium is relatively prominent, in particular in the right VN. Thus, a change in echogenicity was probably mitigated by the hyperechoic epineurium. However, there was a significant side difference of the GSM Index between the left and the right VN within both the MDD and control group. The GSM Index of the left VN was significantly lower than the

right, i.e., the left VN was more hypoechoic, which could be due to a lower number of fascicles in the left VN, which are sheathed by hyperechoic epineurium (10).

We found no significant correlation between MDD symptom severity and VN-CSA or echogenicity. BDI and PHQ-15 ask for symptoms within the last 2 weeks, which reflects rather acute than chronic symptoms. In our findings, the RDD subgroup contributed most to the alterations in VN-CSA. This may suggest that recurrent and chronic courses of MDD alters VN-CSA independently to its current symptom severity.

There are several limitations. Firstly, the MDD group was heterogeneous, comprising patients with FD and RDD, with the RDD subgroup impacting the VN-CSA the most. Further HRUS investigations in MDD should focus on differences between first time, recurrent, and chronic depressive disorders. Moreover, it should be noted that the RDD subgroup presumably underwent a longer period of medical treatment, due to recurrent depressive episodes and long-term intake of antidepressants. We could not rule out that (especially the long-term-treatment with) antidepressants had an influence on the VN alterations, as they may also have anti-inflammatory effects (43, 44). Secondly, the left VN-CSA enlargement was small and thus, it appears unlikely that the VN-CSA may serve as a biomarker for diagnosis or treatment response in MDD on an individual basis. Thirdly, no general procedure of determining echogenicity in HRUS images is established yet. But unlike previous studies (42), we adjusted echogenicity for individual factors during the HRUS examination like changes in gain, depth, and focus by calculating an index, rather than reporting raw values. Finally, there is an ongoing debate whether the sonographically measured VN-CSA reflects the anatomical size of the VN (45).

In conclusion, the enlargement of the left VN-CSA in patients with MDD, and especially in these patients with recurrent depressive disorders, might turn out as a promising imaging biomarker. Possible mechanisms could involve a dysregulation of inflammatory and anti-inflammatory effects of the gut-brain axis. Further sonographic research is warranted, especially over the course of MDD to improve our understanding of the role of the VNs in affective disorders.

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Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Faculty at the University of Leipzig. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FS and JP designed the study. LS, DW, ES, and EB examined the participants. LS, JP, and FS analyzed the data. LS, DW, and JP wrote the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Abnormal voxel-mirrored homotopic connectivity in first-episode major depressive disorder using fMRI: a machine learning approach

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Objective: To explore the interhemispheric information synergy ability of the brain in major depressive disorder (MDD) patients by applying the voxel-mirrored homotopic connectivity (VMHC) method and further explore the potential clinical diagnostic value of VMHC metric by a machine learning approach.

Methods: 52 healthy controls and 48 first-episode MDD patients were recruited in the study. We performed neuropsychological tests and resting-state fMRI scanning on all subjects. The VMHC values of the symmetrical interhemispheric voxels in the whole brain were calculated. The VMHC alterations were compared between two groups, and the relationship between VMHC values and clinical variables was analyzed. Then, abnormal brain regions were selected as features to conduct the classification model by using the support vector machine (SVM) approach.

Results: Compared to the healthy controls, MDD patients exhibited decreased VMHC values in the bilateral middle frontal gyrus, fusiform gyrus, medial superior frontal gyrus and precentral gyrus. Furthermore, the VMHC value of the bilateral fusiform gyrus was positively correlated with the total Hamilton Depression Scale (HAMD). Moreover, SVM analysis displayed that a combination of all clusters demonstrated the highest area under the curve (AUC) of 0.87 with accuracy, sensitivity, and specificity values of 86.17%, 76.74%, and 94.12%, respectively.

Conclusion: MDD patients had reduced functional connectivity in the bilateral middle frontal gyrus, fusiform gyrus, medial superior frontal gyrus and precentral gyrus, which may be related to depressive symptoms. The abnormality in these brain regions could represent potential imaging markers to distinguish MDD patients from healthy controls.

KEYWORDS

major depressive disorder, voxel-mirrored homotopic connectivity, support vector machine, functional magnetic resonance imaging, resting-state

1. Introduction

As a common and debilitating mental disease, major depressive disorder (MDD) is characterized by persistently depressed mood, lack of interest, low energy, and cognitive impairment (1). It has high rates of occurrence, impairment and recurrence. Currently, there are more than around 350 million MDD patients worldwide, and the number of patients is still increasing annually (2). According to the World Health Organization, it is estimated that MDD can reach the first incidence rate among mental disorders in the world by 2030, which will seriously threaten economic development and social stability (3, 4). Previous study showed that MDD was a systematic disease involving in multiple neural circuits, which may be related to genetic factors, environmental factors, psychological factors, and abnormal nerve development (5). Although many studies have been performed on the genetics, neurobiochemistry and neuroendocrinology of MDD (6–10), the pathogenesis is still unclear. The diagnosis of MDD is mainly based on the subjective feelings of patients and the evaluation of depression scales depending on the experience of clinicians. Hence, it is an urgent problem to explore the pathogenesis of MDD and find appropriate objective diagnostic markers.

The traditional imaging indicators of structural magnetic resonance imaging (MRI) are insufficient as markers for MDD diagnosis due to the lack of organic lesions. In recent years, resting-state functional magnetic resonance imaging (rs-fMRI) has developed rapidly, providing new ideas. Rs-fMRI is a non-invasive brain imaging technology reflecting the brain functional activity by measuring the hemodynamic and metabolic changes based on blood oxygen level-dependent (11). It has good repeatability and very high spatial resolution. Additionally, subjects do not need to perform specific tasks during the scanning progress. This technology can explore the pathogenesis of diseases from the perspective of neuroimaging and provide an effective means to find neuroimaging markers. Thus, it has been widely used in the research of neuropsychiatric diseases, such as bipolar disorder (12, 13), autism (14, 15), and Alzheimer's disease (16, 17). It can also be a particularly useful tool for investigating differences between MDD patients and healthy controls (HCs). Previous studies on MDD have revealed that there were structural and functional changes in many brain regions, mainly involving the altered prefrontal cortex, amygdala, hippocampus, corpus striatum, and other brain regions (18–22).

To date, common traditional imaging data analysis methods include amplitude of low-frequency fluctuation (ALFF), regional homogeneity (ReHo), degree centrality (DC) and so on. The methods are mainly utilized to observe brain functional changes in MDD patients from a local perspective. But voxel-mirror homotopic connectivity (VMHC) is a reliable and reproducible measurement from the whole brain level which has been developed rapidly recently (23). It has been applied for neuropsychiatric diseases, such as anxiety disorder (24), autism (25), addiction (26), obsessive-compulsive disorder (27, 28), and Schizophrenia (29). Through the method, the functional connections can be quantified between each voxel in the one hemisphere and the mirror voxel in the other hemisphere at resting state and the intensity reflects the synergy between the hemispheres. In other word, it mainly reflects the information exchange and coordination function between hemispheres by describing the high synchronization of spontaneous activities in the symmetrical regions of the left and right hemispheres. The good

coordination of brain regions between hemispheres plays an important role in integrating cognitive and behavioral related brain functions. Therefore, the study of homotopic functional connection across the cerebral hemispheres might help to further understand the neural mechanisms of MDD.

As a supervised machine learning algorithm, support vector machine (SVM) has unique advantages in dealing with small-sample, high-dimensional, and nonlinear data problems for classification (30). It can determine the optimal segmentation hyperplane in the feature space of data samples to maximize the distance between the hyperplane and various types of samples based on the statistical learning theory and the principle of structural risk minimization. Compared to traditional statistical analysis techniques, it has a simple structure, optimal global solution and high generalization ability as a multivariate pattern analysis approach. Furthermore, it enables programs to learn from data sets and perform tasks without direct users input, which has been applied in the discriminant analysis of various neuropsychiatric diseases (31). As we all know, several studies have reported that VMHC method was applied for the different types of MDD (32–37). However, our study is the first to combine VMHC metric and SVM method to evaluate the classification ability in the first-episode MDD patients without prior assumptions.

In the present study, we aimed to explore the possible neuroimaging mechanism of MDD and identify whether the altered brain regions could be used to discriminate between the first-episode MDD patients and HCs. Firstly, the VMHC approach was applied to identify the functional connectivity between the hemispheres. Next, we used correlation analyses to reveal the relationship between abnormal homotopic connectivity and clinical characteristics. Finally, we discussed the VMHC value in altered brain regions as potential neuroimaging markers by the SVM method. The study will deepen our understanding of neural mechanism changes in MDD.

2. Methods

2.1. Participants

We recruited 48 first-episode MDD patients aged 18–55 years from the traditional Chinese medicine clinic and psychiatric department of Guangdong Sanjiu Brain Hospital, and 52 healthy volunteers from the community through advertisement. This study lasted from May 2017 to August 2018. Before the screening, all subjects signed a written statement of informed consent. This study received ethical approvals from the Ethics Committee of Guangdong Sanjiu Brain Hospital and the Ethics Committee of Southern Medical University. And it was registered on the Chinese clinical trial website (<http://www.chictr.org.cn>, registration number: ChiCTR-IPR-14005427).

All participants included in this study were right-handed. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM-IV-TR) was used to make the diagnoses of the first-episode MDD patients. The participants met the following inclusion criteria: (1) HAMD score of >20; (2) the course of disease of >2 weeks; (3) no psychiatric drugs intake; (4) no neurological or other psychiatric disorders and history of substance dependence; (5) no organic brain diseases; (6) no history of manic or hypomanic episodes; (7) no history of psychiatric illness among their first-degree relatives; and (8) no MRI

contraindications, such as electronic implants, various metals or claustrophobia. Pregnant and lactating women were also excluded.

The HCs met the following inclusion criteria: (1) a comprehensive physical examination conducted before the experiment with all examination results being normal; (2) the total score of HAMD of <7; (3) no mood disorders or neurological disorders; (4) no family history of psychiatric illness among their first-degree relatives; (5) no drugs intake 2 weeks before the experiment; and (6) no MRI contraindications. Furthermore, pregnant and lactating women were excluded. All subjects completed 24 items of the Hamilton Depression Scale (HAMD-24) and Self-Rating Depression Scale (SDS).

2.2. MRI data acquisition

In this study, the MRI imaging data was collected using a GE 3T Signa HDXT superconducting magnetic resonance scanner. During the scanning process, all subjects were instructed to stay awake, lie flat and close their eyes without thinking as much as possible. Their heads were fixed with sponge pads to reduce head movement and equipped with sound insulation earplugs. The sagittal 3D-BRAVO sequence was used for brain 3D-T1WI scanning. The scanning parameters of structural phase were as follows: repetition time (TR)=8.8 ms, time to Echo (TE)=3.5 ms, field of view (FOV)=256 mm×256 mm, voxel size=1 mm×1 mm×1 mm, flip angle=13°, matrix=256×256, slices number=184. Gradient echo planar imaging pulse sequence was used to obtain rs-fMRI imaging data. The front and rear joint lines were taken as the scanning baseline, and oblique axial scanning was performed. The scanning range was from the parietal cranium to the foramen magnum of the subjects. The scanning took about eight minutes and the scanning parameters of functional phase were as follows: TR/TE=2000 ms/30 ms, FOV=24 cm×24 cm, flip angle=90°, slices number=33, slice thickness=5 mm, gap=0.6 mm, matrix=64×64, time points=240.

2.3. Data preprocessing

RESTplus v1.25 (38) and SPM12 software¹ were used for data preprocessing based on MATLAB R2017b platform. The preprocessing steps included: (1) converting DICOM format data to NIFTI format data; (2) removing the first 10 time points to minimize the impact from the initial signal volatility; (3) taking the middle slice as a reference for slice timing; (4) realigning for head movement correction; (5) spatial normalizing by using an echo planar imaging (EPI) template developed by the Canadian Montreal Neuroscience Institute; (6) smoothing by using the 6×6×6 mm³ Gaussian smoothing kernel for improving the signal to noise ratio of data; (7) detrending; (8) nuisance covariates regression including the head movement by using Friston 24 parameter (39); and (9) bandpass filtering to reduce the impact of low-frequency drift and high-frequency noise (0.01–0.08 Hz). One HC and five MDD patients were excluded due to excessive head movements that the translation was >2.5 mm, or rotation was >2.5° in each direction during the scanning process. Consequently, 43 patients and 51 HCs were included in the statistical analyses.

2.4. VMHC calculation

VMHC analysis was performed based on the DPARSF 6.2 software (40). Firstly, the time series of each voxel were extracted in the one hemisphere of the participants. And then, Pearson correlation coefficient was calculated between the time series and the corresponding time series in the symmetric hemisphere. Subsequently, the obtained correlation coefficient was converted to a Z value through Fisher Z transformation in order to generate the VMHC map of the entire brain for each participant. Finally, the average VMHC value of each participant can be extracted for group comparison.

2.5. Statistical analysis

Clinical and neuroimaging data were compared between MDD patients and HCs. SPSS 25.0 software (Chicago, IL) was used to analyze the clinical data of the participants. We analyzed neuroimaging data utilizing RESTplus v1.25 software on MATLAB r2017b platform. The continuous data according with the normal distribution and homogeneity of variance were analyzed by two independent sample t-test, and the categorical data was analyzed by χ^2 test. The mean and standard deviation were expressed for continuous data. Whereas the median and interquartile range were expressed for counting data. We used the gender, age, and education of subjects as covariates for rs-fMRI data if the two groups differed statistically from one another. The test results were corrected by Gaussian random field (GRF) multiple comparison correction. We considered that voxel p of <0.005 and cluster p of <0.05 were statistically significant. The VMHC values of abnormal brain regions were extracted for further correlation analysis and classification.

As a supervised machine learning, the SVM method is a common way to explore the best boundaries between two categories and to solve binary classification problems. The method was applied to test whether extracted VMHC could discriminate between MDD patients and healthy controls. The categorization procedure included training and testing. First, abnormal VMHC were utilized as features to establish the hyperplane and the radial basis function (RBF) kernel was applied in the SVM model. The best parameters for the training dataset, including c (penalty coefficient) and g (gamma), were chosen by the grid search approach. Second, an optimal hyperplane which developed from the training data was applied to a new testing dataset in order to assess the performance of the classification. We used a “leave-one-out” method to produce results with the best levels of accuracy, sensitivity and specificity by the LIBSVM software package in MATLAB r2017b platform. The predictive performance of the SVM model was shown by the area under the receiver operating curve (AUC).

3. Results

3.1. Clinical characteristics

Demographic and clinical characteristics between the two groups were presented in Table 1. The age and sex composition ratios did not significantly differ between the two groups ($p > 0.05$), but there were significant differences in the education level, HAMD-24, and SDS ($p < 0.05$).

¹ <https://www.fil.ion.ucl.ac.uk/spm/>

TABLE 1 Demographics and clinical characteristics of all subjects.

Group	Age (years)	Gender (male/female)	Education (years)	Duration (weeks)	HAMD	SDS
HCS	28.92 ± 7.12	22/29	13.02 ± 2.96	NA	2.53 ± 1.71	25.65 ± 3.70
MDD	31.12 ± 10.35	20/23	11.53 ± 2.50	33.95 ± 41.60	28.14 ± 3.03	75.26 ± 3.78
t/χ^2	-1.176	0.107	2.635	NA	-49.214	-64.094
p value	0.243	0.743	0.01	NA	< 0.0001	< 0.0001

Data are presented as Mean ± SD; N/A, not applicable.

3.2. VMHC comparison

Individual whole-brain VMHC values of MDD patients were compared between MDD patients and HCs. Additionally, we took the education level as a covariate in the statistical analysis of rs-fMRI data. MDD patients had lower VMHC values in the bilateral middle frontal gyrus (MFG), fusiform gyrus (FG), medial superior frontal gyrus (MSFG) and precentral gyrus (PG) (GRF correction, voxel $p < 0.005$, cluster $p < 0.05$, cluster size > 64) relative to HCs, as shown in Table 2 and Figure 1.

3.3. Correlations analyses

Figure 2 showed the correlation analysis between the VMHC and clinical characteristics. The VMHC values of different brain regions of all subjects were extracted by using RESTplus V1.25 software based on MATLAB r2017b platform. A positive correlation was observed between the VMHC value of the bilateral fusiform gyrus and HAMD ($r = 0.3723$, $p = 0.014$).

3.4. Support vector machine

The decreased VMHC values of these four brain regions in MDD patients were analyzed by the SVM method. The four clusters were used as features separately or together. The receiver operating curves (AUCs) of models were as follows: MFG of 0.86, FG of 0.82, MSFG of 0.79 and PG of 0.76. The decreased VMHC in the MFG showed the highest diagnostic accuracy of 81.91%, with a sensitivity of 74.42% and a specificity of 88.24%. Based on the results of the SVM, the combination of decreased VMHC in the four clusters produced the highest AUC of 0.87, with an accuracy of 86.17%, a sensitivity of 76.74%, and specificity of 94.12% together (See Table 3 and Figure 3).

4. Discussion

Our research compared the brain activity of MDD patients with that of HCs using the VMHC method. The results showed that compared to the HCs, the MDD group had decreased VMHC in the bilateral MFG, FG, MSFG, and PG which represented the decreased synchronization and information exchange. Additionally, a positive correlation was found between VMHC value of the bilateral FG and HAMD scores in MDD patients. Based on the SVM results, a combination of decreased VMHC value in the four clusters had relatively the highest AUC, sensitivity, specificity and accuracy.

TABLE 2 Abnormal brain regions in the MDD patients compared to HCs.

Regions	Cluster size	Peak T value	MNI Coordinate (mm)		
			X	Y	Z
MFG	1773	-5.5839	±42	24	42
FG	236	-4.9282	±27	-78	-15
MSFG	131	-5.3559	±9	60	18
PG	117	-4.7597	±48	-18	42

MFG, middle frontal gyrus; FG, fusiform gyrus; MSFG, medial superior frontal gyrus; PG, precentral gyrus (voxel $p < 0.005$, cluster $p < 0.05$, GRF correction, cluster size > 64 voxels).

The MSFG and the MFG are both important components of the prefrontal cortex which participate in a variety of neural functions. The MSFG is responsible for working memory, stress perception, regulation of loss aversion and behavior (41). Stress perception refers to the ability to perceive various negative external factors, which often serves as an important factor in predicting the occurrence of depression. The involvement of the MFG in emotional processing is related to psychological resilience (42, 43). The MSFG and MFG are important components of the default network and frontal parietal network. The default network plays an important role in emotional processing, self-referencing psychological activities and recalling previous experiences (44, 45). And the frontoparietal network is an important cognitive functional network that participates in controlling and regulating cognitive activities in the brain (46). The depressed patients showed substantial changes in the BOLD signal in the left MSFG relative to HCs (47) and the MSFG was demonstrated a high level of diagnostic accuracy in the late-life depression (48). Additionally, Lan et al. observed that MDD group had higher fALFF value in the right MFG (49). The MDD patients with somatic symptoms exhibited lower ReHo value in the right MFG (50) and the depressive patients had less pronounced activation of MFG in response to both positive and negative images (51). Several studies found that the abnormal interhemispheric homotopic functional connectivity in the bilateral MSFG and MFG in different types of depressive group, such as MDD with and without anhedonia, recurrent MDD and MDD with gastrointestinal symptoms (52–54). We also discovered that first-episode MDD group had lower VMHC in the MSFG and MFG compared to HCs. This indicated the importance of the homotopic connectivity between these two brain regions in the pathogenesis of depression.

The FG, known as the lateral occipitotemporal gyrus, is the cerebral cortex between the temporal lobe and the occipital lobe (55). The FG, as a crucial component of the visual recognition network, is mainly responsible for the perception and processing of emotion during face stimulus presentation. It involves in higher-order vision processing and

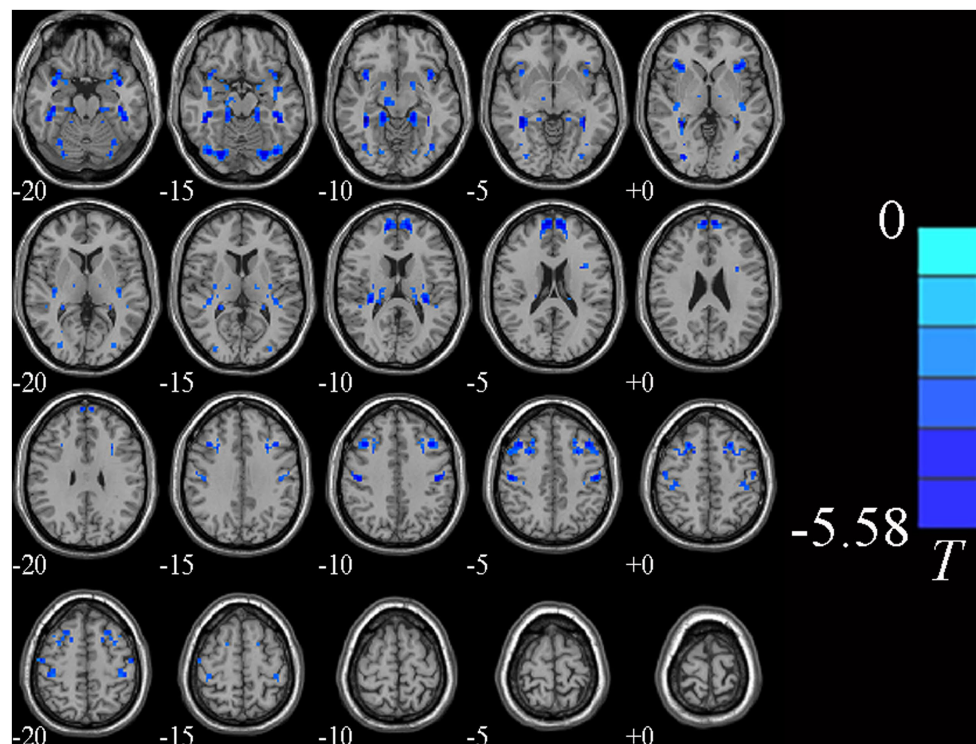


FIGURE 1

Brain regions showing significantly different VMHC values between two groups. Cold colors indicate decreased VMHC values (voxel $p < 0.005$, cluster $p < 0.05$, GRF correction, cluster size > 64 voxels).

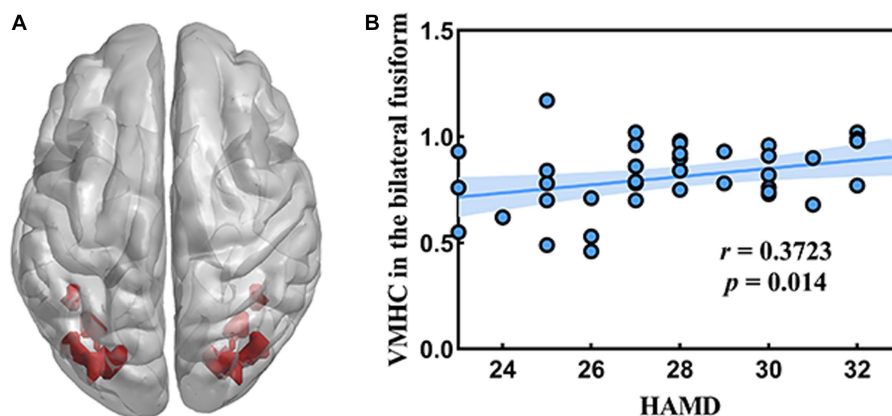


FIGURE 2

Correlation between the VMHC value in the bilateral fusiform gyrus and HAMD. (A) The location of bilateral fusiform gyrus in the whole brain. (B) The result of correlation analysis.

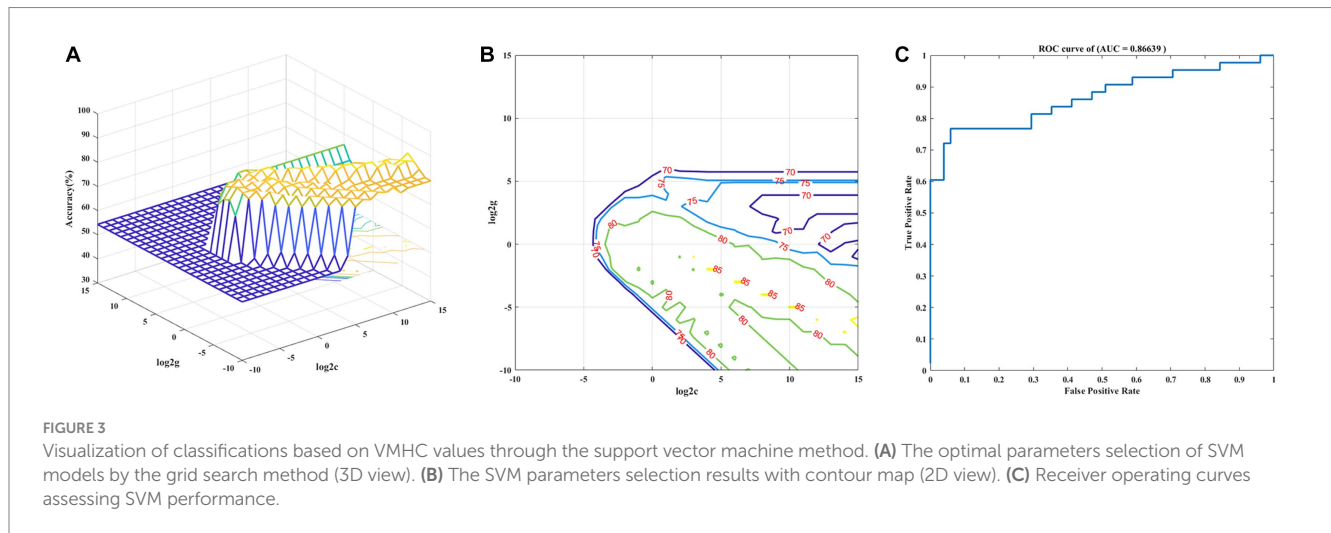
is probably most well-known for its involvement in visual face processing, although it also plays an important role in the visual processing of body parts, objects, places and word forms (56). K and V et al. reported that MDD patients had abnormal volume in the FG related to alexithymia in comparison with healthy controls (57). And the patients with MDD have shown significantly decreased local gyrification index in the right FG and decreased functional connectivity between the right FG, right superior temporal gyrus and sensorimotor areas (precentral and postcentral gyrus) (58). Moreover, Korgaonkar et al.

revealed decreased fractional anisotropy in the temporal lobe involving the FG in melancholic MDD (59). Subjects with cognitive vulnerability to depression have the increased ALFF in the left FG (60) and increased fALFF value in the FG was related to some depressive symptoms in MDD patients (61). Otherwise, one study showed that MDD group had decreased ReHo values were seen in the right FG compared with HCs (62). The MDD patients exhibited that significant decreased VMHC in the FG and a negative correlation was found between VMHC of the FG and illness duration relative to healthy controls (32, 34). Interestingly, the

TABLE 3 SVM classification performances.

Regions	Best c	Best g	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC
MFG	0.5	8	81.91	74.42	88.24	0.86
FG	512	32	80.85	76.74	84.31	0.82
MSFG	0.25	8	76.60	65.12	86.27	0.79
PG	32	512	76.60	79.07	74.51	0.76
All	32,768	0.0156	86.17	76.74	94.12	0.87

MFG, middle frontal gyrus; FG, fusiform gyrus; MSFG, medial superior frontal gyrus; PG, precentral gyrus. A combination of all clusters built the best SVM model. The best c was 32,768; The best g was 0.0156; The AUC of best model was 0.87.



VMHC value of the bilateral FG was positively correlated with the HAMD in our study. This may be the transitional stage of decompensatory period. The consistency and synergy of bilateral FG was enhanced with the more severe depression, which may be related to the compensatory enhancement of information exchange and integration.

The PG was part of the central executive network. Several studies have suggested that the PG changed in patients with depression. L. Wang et al. observed that MDD patients had the significant altered ALFF and fALFF value in the precentral gyrus (63). There were significant negative correlations between the abnormal fALFF in the right precentral gyrus and the change of Beck Scale for Suicidal Ideation at baseline and between the abnormal ALFF in the right precentral gyrus and the change in HAMD. Furthermore, reduced ReHo value in the right precentral gyrus have been reported in the unipolar depression group (64). The somatic depression also exhibited that lower ReHo value in the left precentral gyrus and ReHo value in the left precentral gyrus was positively correlated with cognitive factor scores of the HAMD-17 compared to non-somatic depression (50). Additionally, Shan et al. found that the melancholic patients displayed the decreased VMHC value in the precentral gyrus and the SVM analysis results showed that the VMHC value between the bilateral precentral gyrus may serve as underlying imaging indicators to distinguish melancholic patients from non-melancholic MDD (36). The Treatment Resistant Depression group had significantly lower VMHC values in the precentral gyrus as compared to the treatment sensitive depression group (33). Our results revealed that the first-episode MDD patients exhibited aberrant VMHC value in the precentral gyrus, which was roughly consistent with the previous findings even though different

types of depression. Decreased coordination was discovered throughout other brain areas, involving in bilateral insular, putamen, posterior cingulate cortex, cuneus and superior temporal gyrus (35, 65, 66). The different results may be related to the sample size, the severity and course of depression, medication or other interventions, multiple comparison correction methods and statistical threshold.

At present, clinical symptoms are mostly used for MDD diagnosis. Machine learning is an objective measurement that may might increase the accuracy of MDD diagnostic reliability. The ROC analysis was carried out to assess the effectiveness of the SVM classifier. The SVM model in our study showed good performance for MDD, with an accuracy of 86.17%, sensitivity of 76.74%, specificity of 94.12% and AUC of 0.87 based on the leave-one-out cross validation technique. As a result, aberrant VMHC signal values in these brain regions may serve as potential imaging markers for discriminating MDD patients from HC. This study had some limitations. Firstly, the sample size was small, which might reduce the statistical effectiveness and affect the stability of the results. Secondly, the study had a cross-sectional design, lacking longitudinal observation of depression. These patients can be followed up to elaborate on the pathological mechanism of the disease in the future. Thirdly, a weak correlation existed between the depression scales and the VMHC value. This may be related to the small sample size and the depression levels of the included patients. In conclusion, we found the altered VMHC of the MFG, FG, MSFG, and PG in MDD patients, indicating that the impairment of these brain areas may contribute to the pathogenesis of depression. In the future, we can combine T1 and DTI technology to further explore the neuroimaging mechanism of depression from a multimodal perspective.

5. Conclusion

In our study, MDD patients exhibited decreased VMHC value in the MFG, FG, MSFG and PG. The VMHC value of FG was positively correlated with the total HAMD scores. Moreover, SVM analysis results showed that a combination of the VMHC values of all clusters demonstrated the highest area under the curve (AUC), which may be a potential neuroimaging marker for the MDD. According to this study, it highlighted the importance of decreased coordination between hemispheres in these brain regions into the pathophysiology of MDD and VMHC values could also serve as a potential imaging biomarker for diagnosing MDD.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by this study received ethical approvals from the Ethics Committee of Guangdong Sanjiu Brain Hospital and the Ethics Committee of Southern Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZL designed the study. YB, WY, SW, TX, YW, SH, CZ, SX, SK, and WK recruited the patients and collected the fMRI data. QC sorted all imaging data and carried out the analysis and wrote the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Is brain perfusion correlated to switching mood states and cognitive impairment in bipolar disorder type I? A longitudinal study using perfusion imaging approach

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Type I Bipolar disorder (BD-I) is a neuropsychiatric disorder characterized by manic or mixed-featured episodes, impaired cognitive functioning, and persistent work and social functioning impairment. This study aimed to investigate within-subject; (i) differences in brain perfusion using Single-photon emission computed tomography (SPECT) between manic and euthymic states in BD-I patients; (ii) explore potential associations between altered brain perfusion and cognitive status; and (iii) examine the relationship between cerebral perfusion and mania symptom ratings. Seventeen adult patients diagnosed with BD-I in a manic episode were recruited, and clinical assessments, cognitive tests, and brain perfusion studies were conducted at baseline (mania state) and a follow-up visit 6 months later. The results showed cognitive impairment during the manic episode, which persisted during the euthymic state at follow-up. However, no significant changes in brain perfusion were observed between the manic and euthymic states. During mania, trends toward decreased perfusion in the left cerebellum and right superior parietal lobule were noted. Additionally, trends indicated a higher perfusion imbalance in the left superior and middle frontal gyrus during mania and the right superior and middle frontal gyrus during euthymia. No significant correlations existed between brain perfusion, mania symptom ratings, and cognitive performance, indicating that symptomatology might represent more than neural hemodynamics. These findings suggest that cognitive impairment may persist in BD-I patients and highlight the need for therapeutic interventions targeting cognitive deficits. More extensive studies with extended follow-up periods are warranted further to investigate brain perfusion and cognitive functioning in BD-I patients.

KEYWORDS

bipolar disorder, SPECT, brain imaging, cognitive function, neuroimaging, nuclear medicine

1. Introduction

Type I Bipolar disorder (BD-I) is a common neuropsychiatric disorder with a lifetime worldwide prevalence of approximately 1% (1). It is characterized by at least one lifetime manic or mixed-featured episode, and it may be accompanied by impaired attentional processing, executive function, verbal memory, and persistently impaired work and social functioning (2, 3); these deficits can be observed in all stages, including euthymia (phase of normality between episodes of mania or depression) (4–6). Brain lesions evidence shows that mania occurs in up to 30% of BD-I patients with basal ganglia calcification, associated with right-sided destructive lesions and with the left-sided epileptogenic lesion, deriving a laterality imbalance (7). However, functional neuroimaging studies have found previous alterations in limbic structures and prefrontal areas, possibly related to cognitive impairment (8). Nonetheless, the current evidence to determine this relationship is inconclusive because it is based chiefly on cross-sectional designs in various patient groups. This approach limits comparison (and correlations) between the different clinical states due to inter-subject differences (9).

Longitudinal studies investigating subjects during manic, euthymic, and depressed episodes promise to capture disease-specific within-subject alterations, as the switch between mood states is a hallmark of BD-I patients. Such designs are challenging, and only a few studies show images of subjects across mood episodes (10–14), and these studies used Magnetic Resonance Imaging to study functional activation and connectivity changes. Cerebral blood flow (CBF) abnormalities have been previously described in patients with Major Depressive Disorder (MDD) and Schizophrenia (15–17). A systematic review of 33 studies compared CBF findings in BD and healthy control subjects (HC) at rest and in response to cognitive and emotional tasks; the most consistent finding was reduced CBF in BD in the cingulate gyrus, frontal, and anterior temporal regions during either depressive or manic stages, compared to healthy controls. However, longitudinal measures of CBF across mood states are rare: Most relevant to the present study, in longitudinal studies contrasting symptomatic (mania or depression) with euthymia, a right–left asymmetry in anterior temporal lobes was observed in the pathological mood states (18). A review of perfusion-weighted magnetic resonance imaging studies in BD found results that supported the presence of hyper-perfusion in the cingulate cortex and frontotemporal regions, as well as the company of hypo-perfusion in the cerebellum in BD subjects when compared with HC and subjects with unipolar depression (19). A study of perfusion fluctuation and perfusion connectivity in BD subjects measured by dynamic arterial spin labeling found that BD subjects exhibited significantly increased perfusion fluctuations in the left fusiform and inferior temporal regions and marginally increased perfusion fluctuations in the right temporal pole and inferior temporal areas, and increased perfusion connectivity between anterior cingulate cortex and the occipitoparietal cortex. Positive symptoms were negatively associated with anterior cingulate cortex perfusion connectivity to the right orbitofrontal and superior frontal regions and right orbitofrontal and inferior frontal regions (20).

Regarding possible changes in brain perfusion, as they relate to cognitive function, prior results have been mixed: Regarding CBF in relation to cognitive and emotional tasks comparing BD and HC subjects, it was found that decreased CBF in BD group during memory

tasks, increased CBF in prefrontal and limbic regions in BD group and parietal and premotor areas of HC group during serial reaction time tasks, decreased CBF in the dorsolateral prefrontal cortex in BD group during verbal learning tasks, as well as increased CBF in dorsal anterior cingulate cortex regions and decreased CBF in left frontal pole in BD group during decision-making tasks. No differences were found between the groups in studies that used color-word inhibition and verbal fluency tasks. In studies without a HC group, a correlation was found between worse performance on memory and verbal learning and low frontal CBF; also, the psychomotor performance was related to greater anterior temporal CBF in baseline CBF and subsequent cognitive performance with increased CBF in left inferior opercular frontal gyrus in a before and after 4-week cognitive training study. Correlations between CBF and cognitive performance were reported, noting that lower CBF was associated with poorer performance on measured memory tasks, verbal learning, response inhibition, and complex abstraction.

In a previous study, we began exploring cognitive status and brain perfusion (measured by SPECT) during a manic episode in 10 patients with BD-, reporting a positive association between cognitive functioning impairments (verbal learning, verbal fluency, and processing speed) with perfusion in the right temporal pole and a negative association with perfusion in the orbitofrontal cortex and subgenual cingulate cortex, from right hemisphere (21). We expand on these results using a larger sample size, longitudinal design, and quantitative voxel-wise neuroimaging analysis.

The present study aimed to describe within-subject differences in brain perfusion between mania and euthymia; specifically, we explored if the switch from mania to euthymia incurred changes in the laterality of perfusion, with the hypothesis that the mania state would be associated with a higher imbalance in perfusion, favoring relatively higher perfusion of the left cerebrum, based on prior neuroimaging reports (7, 22). Additionally, we sought to explore potential associations between altered brain perfusion reductions in CBF in cingulate, frontal, and anterior temporal regions, as per the prior literature and cognitive status, capitalizing on the within-subject design. Lastly, we characterized the relationship between cerebral perfusion and mania symptom ratings in the whole sample.

2. Methods

2.1. Subjects

Between March 2015 and March 2019, we recruited 17 adult patients diagnosed with BD-I undergoing a moderate or severe manic episode according to the Young Mania Scale (YMRS; YMRS score ≥ 20) (23, 24), in the National Institute of Psychiatry Ramón de la Fuente Muñiz (INPRFM). Participants were diagnosed according to the DSM IV-TR criteria (25) by an experienced psychiatrist using the South and Central America version of the International Neuropsychiatric Interview (MINI) (26). We included participants with BD-I diagnoses of no longer than 5 years, without current pharmacological treatment, and with no history of electroconvulsive therapy for at least 6 months before the initial evaluation. Patients with a score ≥ 19 on the Montgomery-Asberg Depression Scale for Depression (MADRS) (27), with neuropsychiatric comorbidities, uncontrolled medical conditions, alcohol or other substance use, as

well as pregnant or lactating women, were excluded. This study was approved by the Institutional Ethical Review Board of the National Institute of Psychiatry “Ramón de la Fuente Muñiz.” According to the Institution’s guidelines, all participants or legal representatives received a study explanation and signed informed consent before entering the study.

2.2. Clinical and cognitive assessments

A complete medical history, a physical examination, a hematological biochemical evaluation (blood biometry, blood chemistry, liver function, and thyroid function), a general urine examination, and an electrocardiogram were obtained for each participant. Regarding cognitive functioning, we assessed immediate verbal learning, fluency, and processing speed. Ten subjects were evaluated using the Immediate Verbal Learning Test (VLT-I), the Verbal Fluency Test (VFT), and the Processing Speed Test (PST) subtests of the Cognitive Impairment in Psychiatry (SCIP-S) Screen Scale Spanish version (28). Seven subjects were assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R) (29) to assess immediate verbal learning, the animal categorical fluency test to assess verbal fluency, and the Brief Assessment of Cognition in Schizophrenia-Symbol Coding test (BACS-SC) (30) to assess processing speed. These assessments were performed at baseline (mania state) and follow-up visits 6 months later. The test scores were normalized and standardized according to each instrument’s cut points using the following formula: $a/b = c/x$.

2.3. Neuroimaging protocol

Perfusion studies were performed on participants in a manic state at the INPRFM. The protocol was performed during the resting state using two-head SPECT-CT (PRECEDENCE-Philips). A radiopharmaceutical 925 MBq of Tc99m-ethyl cysteine iReimer (Neurolite R Accesofarm) was administered for 40–45 min.

2.4. Statistical analysis

For the descriptive analysis of categorical variables, absolute and relative frequencies were obtained. For quantitative variables, means, medians, and their respective dispersion measures were calculated. The normality of the distribution was evaluated graphically and through the Shapiro–Wilk test. The Spearman rank correlation (correlation between cognitive domains and clinical variables) was performed. A $p < 0.05$ was considered statistically significant with a 95% confidence interval. Due to the exploratory nature of this analysis, we did not correct by multiple comparisons to avoid the type II error. The analysis was performed in the statistical software Stata (version 15.0).

The brain imaging data were modeled in SPM 12 using a multiple linear regression approach. Individual subjects’ mania- and euthymia—SPECT perfusion images were co-registered to compute an average image. This average was normalized to MNI space, and transformations were applied to the mania- and euthymia images, thus avoiding an order bias in co-registration. The spatially normalized

images were further smoothed with a 16 mm full-width-half-max filter. The preprocessed images were entered in a repeated measures t -test model, controlling for scan global intensities using an ANCOVA regressor.

To analyze laterality effects (the main aim of this study), the raw mania and euthymia-perfusion images were right–left flipped, co-registered to the non-flipped average, and preprocessed as above. Changes in the laterality of perfusion between mania and euthymia were determined by contrasting non-flipped and converted perfusion images in mania versus those in euthymia. Lastly, we utilized the entire sample of subjects evaluated in the mania state to assess the potential correlations between brain perfusion and cognitive outcomes, as well as with symptoms, as rated on the YMRS scale.

For all analyses, the cluster forming threshold was set at $p < 0.001$, and significance was set at $p < 0.05$, corrected by family-wise error rate. Trends for clusters with more than five contiguous voxels at $p < 0.001$, not surviving correction for multiple comparisons, are also reported.

In addition to the above analysis, we further explored results using threshold-free cluster enhancement (TFCE), an approach introduced to increase the sensitivity of voxel-based analyses applying 5,000 permutations and optimizing voxel-level thresholding (31), and by defining regions of interest based on prior literature in the cingulate, frontal lobe, and the temporal poles, determined using the WFU_pickatlas tool (32) and the A.A.L. library (33).

3. Results

3.1. Participants and ratings

We included 17 patients in the study, 14 women and three men. The mean age was 41.2 (SD = 15.09; Table 1). The cognitive domains of immediate verbal learning, verbal fluency, and processing speed demonstrated performance below the typical threshold at baseline (Table 2). Additionally, there was no observed correlation between YMRS scores and cognitive functioning.

During the follow-up, 6 months later, eight out of the 17 patients were evaluated (nine participants discontinued their participation due to personal reasons and time availability). An expected significant difference between baseline and follow-up measurements was found in YMRS scores ($p < 0.001$). No differences were found between the cognitive outcomes and the rest of the clinical assessments, even

TABLE 1 Clinical and sociodemographic characteristics.

Variable		<i>n</i>	%
Sex	Women	14	82.3
	Men	3	17.6
		Mean	Min-Max
Age		37	20–67
Years of schooling		13.47	5–19
Duration of the last manic episode (weeks)		4.02	1–16
Time since diagnosis (years)		2.5	0–4
Number of previous episodes of mania		1.29	1–3
Number of prior episodes of depression		1.11	0–4

TABLE 2 Clinical and cognitive functioning.

SCALES	The score during the episode of Mania <i>n</i> = 17	Score on 6-month follow-up <i>n</i> = 8	Interpretation of the results
	Stocking (min-max)	Stocking (min-max)	
MADRS	5.17 (0–14)	5.82 (0–11)	≥ 35: Severe depression
			20–34: Moderate depression
			7–19: Mild depression
			≤ 6: Depression in recovery
YMRS	32.82 (20–56)	1.87 (0–4)	≤6: Euthymia
			7–20: Mixed episode
			>20: Manic episode
BPRS	32.17 (20–47)	25.12 (21–28)	0–9: Absence of the disorder.
			10–20: Mild disorder
			≥21: Severe disorder
			Normal values*
Immediate verbal learning	18.32 (7–27)	17.12 (9–25)	<21
Verbal fluency	16.35 (6–28)	19.12 (12–27)	<19
Processing speed	9.95 (5–15.8)	9.62 (5–14)	<12

MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale; BPRS, Brief Psychiatry Rating Scale; SCIP-I, screen for cognitive impairment in psychiatry.

*Reference values are taken from Rojo et al. (34).

though all subjects were euthymic, and none of them were depressed according to the MADRS scores. As no significant changes in cognition were discerned between the mania and the euthymia, we did not pursue the planned correlation analyses of changes in cognition about changes in perfusion. Pharmacological treatment at follow-up are described in [Supplementary Table 1](#).

Brain perfusion was not significantly different between the mania and the euthymia state. However, at a less stringent threshold ($p < 0.001$, not corrected for multiple comparisons), a trend toward decreased perfusion in the mania state was observed in the left cerebellum and the right superior parietal lobule, see [Table 3](#) and [Figure 1](#).

The TFCE and ROI approaches did not yield any further significant findings.

3.2. Laterality of mania

There were no significant differences in perfusion laterality imbalance, contrasting the mania and euthymic states. At a less stringent threshold ($p < 0.001$, not corrected for multiple comparisons), a trend was observed in that the mania state was associated with a relative imbalance suggesting higher perfusion in the left superior and middle frontal gyrus, see [Table 3](#). Similarly, the right superior and

middle frontal gyrus observed a trend toward more significant asymmetry in the euthymia state.

3.3. Relation between perfusion and mania ratings

For the entire sample evaluated only in the mania state ($n = 17$), there were no significant correlations to the YMRS scale. At a less stringent threshold ($p < 0.001$, not corrected for multiple comparisons), a trend was observed toward a positive correlation between YMRS ratings and perfusion of the left occipital fusiform gyrus ([Table 3](#)).

4. Discussion

This study aimed (i) to investigate the differences in brain perfusion between manic and euthymic states in BD-I patients, (ii) to explore potential associations between altered brain perfusion and cognitive status, (iii) and examine the relationship between cerebral perfusion and mania symptom ratings. We detected cognitive impairment during the manic episode, which persisted during the euthymic state at follow-up. However, no significant changes in brain perfusion were observed between the manic and euthymic states. We discuss each of these findings below.

4.1. Cognitive function in BD patients during mania

During the manic episode, immediate verbal learning, fluency, and processing speed were found below the normalized values for each subscale. These results agree with those reported in a systematic review, where it was found that during the manic episode, patients showed significant dysfunctions in attention, language, memory, and executive functions (13). However, in the eight subjects who also participated in our follow-up visit, we did not observe any changes in cognitive function between the manic episode and euthymia, suggesting that cognitive function did not improve in euthymia in BD-I (4, 35).

4.2. Changes in brain perfusion

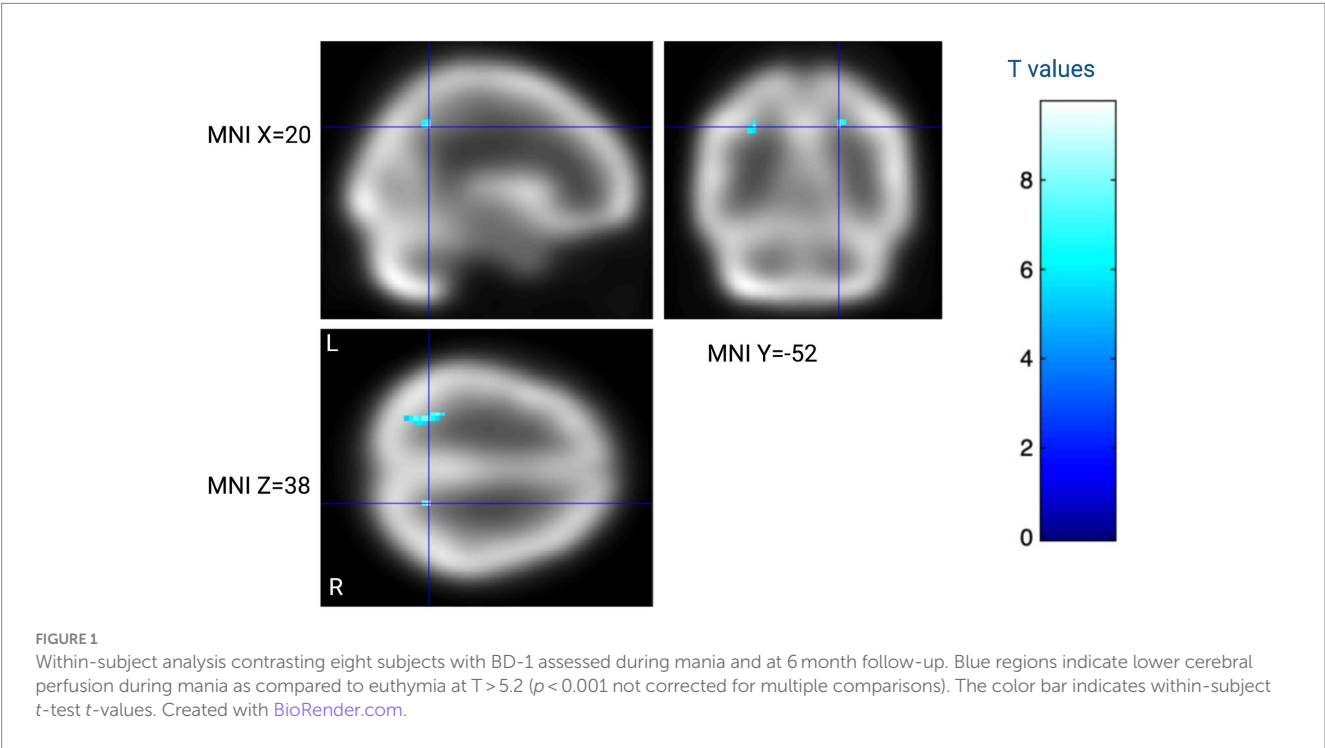
There were no significant changes in measured cerebral perfusion between the manic state at follow-up euthymia. Several trends were, however, observed, with reduced perfusion of the right parietal cortex during mania and evidence of more significant left–right perfusion imbalance during mania, particularly in the left superior and middle frontal gyrus. We note that these trends correspond to a general pattern of mania associated with right-hemisphere hypofunction and left-hemisphere hyperfunction (7, 22), *ad hoc* to our hypothesis; yet, these trends should be interpreted cautiously.

We also did not observe significant correlations between the YMRS score and cerebral perfusion in the mania state. A trend toward a negative correlation between YMRS ratings and perfusion of the left occipital fusiform gyrus was observed. Only a few data implicate selective disturbances in the occipital cortex in BD-I, possibly indicating that this trend should be explored in more detail (36, 37).

TABLE 3 Brain perfusion results.

Analysis	Contrast	Cluster size	T	Z (eq)	p(unc)	MNI			Brain region
						x	y	z	
Repeated <i>t</i> -test on perfusion	Mania < euthymia	6	9.7	3.98	< 0.001	20	−52	38	Right precuneus
		28	8.35	3.77	< 0.001	−28	−52	38	Left superior parietal lobule
		27	6.78	3.48	< 0.001	−8	−74	−45	Left cerebellum lobule VIII-X
		5	6.05	3.31	< 0.001	12	−41	45	Right precuneus
		28	8.35	3.77	< 0.001	−28	−52	38	Left superior parietal lobule
Laterality-by-state	Mania (left vs. right) > Euthymia (left vs. right)	42	4.81	3.77	< 0.001	−20	42	26	Left superior and middle frontal gyrus
		7	4.11	3.38	< 0.001	−35	22	−12	Left anterior insula
	Mania (left vs. right) < euthymia (left vs. right)	27	4.58	3.65	< 0.001	23	44	26	Right superior and middle frontal gyrus
Symptom correlation	Positive correlates to YMRS	40	4.18	3.31	< 0.001	−33	−79	−10	Left occipital fusiform gyrus

YMRS, young mania rating scale; MNI, coordinate system of the Montreal Neurological Institute and Hospital.



4.3. Cognitive functioning and clinical variables at 6-month follow-up

This study found that, even if the manic symptoms improved, cognitive functioning 6 months later was still impaired. These findings coincide with those found in a prior meta-analysis in which patients

with euthymia showed impairment in verbal learning functions and immediate and delayed verbal memory, as well as in tests of executive functions related to problem-solving, verbal interference, and attention change tasks. It should be noted that this systematic review only included cross-sectional studies of patients in different phases of BD, without follow-up (9).

Some factors have been studied to explain the persistent cognitive impairment in BD-I patients, such as the number and severity of episodes, considering chronic patients or patients having a history of multiple episodes suffer from more significant cognitive deficits, age at illness onset, presence of psychotic symptoms, years of stabilization, and pharmacological treatment, since medication may negatively affect cognitive performance (38). However, the population sample we examined had less than 5 years since BD-I diagnosis, with an average of 2.5 years and 1.29 throughout their lifetime; this suggests that cognitive impairment may start early during the disorder. Other studies have found that cognitive impairment may be an endophenotype for BD, as evidence shows that psychomotor speed and response inhibition are observed in unaffected relatives and offspring of BD-I patients (39). Furthermore, some studies have found that cognitive deficits are still evident in euthymic medication-free patients (35). Around two-thirds of BD-I patients experience cognitive problems, directly impacting their ability to function socially and occupationally. Moreover, a pattern of cognitive decline may increase the likelihood of recurring episodes (40).

Open and controlled studies have been made to investigate the outcomes of cognitive rehabilitation interventions for BD patients. Some of these interventions have shown promising results in reducing depressive symptoms and improving executive functions (41). However, more research on cognitive impairments is needed to expand treatment options.

We found no significant correlation between brain perfusion and YMRS score or cognitive performance at baseline or follow-up. The limited sample size might explain this, but in light of recent large-scale, complex phenotypes like mania symptoms or cognition may not lend themselves to simple linear relationships (42).

4.4. Clinical significance

A significant decrease in the YMRS scale score and overall clinical improvement was found at follow-up. However, we found no difference in cognitive performance. BD is accompanied by neurotoxic processes that can accelerate the mechanisms of normal aging (43). Neurostructural, alterations in oxidative stress and amyloid metabolism, immune dysregulation, immunosenescence, neurotrophic deficiencies, and telomere shortening have been found in patients with BD-I (44–47). Although these results could be associated with the pharmacological treatment of the patient or with the recovery of global and cognitive functioning after a manic episode, perhaps taking more than 6 months, it is also possible that cognitive alterations are persistent traits, present even without affective symptoms (11, 39, 48, 49).

Our outcomes highlight the relevance of developing new therapeutic strategies aimed at improving and maintaining the cognitive functioning of these patients, as well as possible neuroanatomical targets to direct treatments based on the clinical state of the patients. There is no currently available robust evidence of therapeutic interventions targeting cognitive deficits. Regarding pharmacotherapy, lurasidone, vortioxetine, omega-3 fatty acids, modafinil, vitamin D, and aspirin are currently under investigation in BD-I (3). Functional remediation appears as an excellent option to alleviate psychosocial outcomes in bipolar patients, with an effect that seems to remain in the long term. However, current evidence is insufficient and additional studies are required to prevent neurocognitive impairment and the associated disability in BD patients (50).

4.5. Strengths and limitations

Some of the limitations of this study were having a small sample size and the high rate of loss to follow-up (47%). It was impossible to control the pharmacological treatment of patients after the manic episode; this is shown in [Supplementary Table 1](#). Two sets of instruments were used to assess cognitive function among the participants, and scores and cut points were calculated proportionally according to the SCIP-S sub-scores. However, this is one of the few studies that have tracked BD-I patients longitudinally and evaluated brain perfusion and cognitive functioning, which may provide more information about the pathophysiology of cognitive impairment in BD-I.

5. Conclusion

This study found limited evidence of alterations in brain perfusion during manic episodes, partly supporting BD-I's laterality hypothesis. There was evidence of cognitive impairment during mania, and although patients changed to euthymia, their cognitive functioning did not improve after 6 months. Studies in larger populations with extended follow-up periods are needed to explore brain perfusion and cognitive functioning changes in patients with BD-I.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The Instituto Nacional de Psiquiatría Ethics Committee Board reviewed and approved this study. The study was conducted per the Federal legislation and institutional policies. Written informed consent was obtained from participants and family members.

Author contributions

ME-G, CL, VG, GC-K, KP-B, LM-Q, and MF have been involved in interpreting the results, drafting the manuscript, revising critically for important intellectual content, giving final approval of the version to be published, and agreeing to be accountable for all aspects of the work. CL performed the brain perfusion analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2023.1244134/full#supplementary-material>

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Distinguishing functional and structural MRI abnormalities between bipolar and unipolar depression

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Background: This study aims to investigate the underlying characteristics of spontaneous brain activity by analyzing the volumes of the hippocampus and parahippocampal gyrus, as well as the fractional amplitude of low-frequency fluctuation (fALFF) and regional homogeneity (ReHo), in order to differentiate between bipolar disorder (BD) and unipolar depressive disorder.

Methods: A total of 46 healthy controls, 58 patients with major depressive disorder (MDD), and 61 patients with BD participated in the study and underwent resting-state functional magnetic resonance imaging (rs-fMRI) scans. The researchers calculated the differences in volume, fALFF, and ReHo values among the three groups. Additionally, they conducted correlation analyses to examine the relationships between clinical variables and the aforementioned brain measures.

Results: The results showed that the BD group exhibited increased fALFF in the hippocampus compared to the healthy control (HC) and MDD groups. Furthermore, the ReHo values in the hippocampus and parahippocampal gyrus were significantly higher in the BD group compared to the HC group. The findings from the person correlation analysis indicated a positive relationship between ReHo values in the hippocampus and both HAMD and HAMA scores. Moreover, there was no correlation between the volumes, fALFF, and ReHo values in the hippocampus and parahippocampal gyrus, and cognitive function levels (RBANS).

Conclusion: Taken together, these aberrant patterns of intrinsic brain activity in the hippocampus and parahippocampal gyrus may serve as quantitative indicators for distinguishing between BD and unipolar depression.

KEYWORDS

bipolar disorder, major depressive disorder, fractional amplitude of low frequency fluctuation, regional homogeneity, magnetic resonance imaging – high field

Introduction

Bipolar disorder (BD) is a complex psychiatric condition characterized by alternating episodes of depression and manic or hypomanic states (1), often accompanied by cognitive impairments and impulsive behaviors related to emotions (2). The challenge lies in differentiating BD from major depressive disorder (MDD)

(3), as symptoms of depression in BD can often be mistaken for MDD. Unfortunately, misdiagnosis is common, with many BD patients being incorrectly identified as having MDD for extended periods of time (4). This can have serious consequences, including worsened manic symptoms, decreased quality of life, and an increased risk of suicide (5). To ensure accurate diagnosis, clinicians need to be aware of the comorbidities associated with BD and develop means to distinguish it from other disorders. Differentiating between bipolar and unipolar depression based solely on clinical observations can be challenging, leading researchers to explore neural markers through neuroimaging in order to distinguish between the two (6). Therefore, it is necessary to identify biomarkers associated with bipolar depression and develop clinically applicable diagnostic tools to shed light on its potential pathogenesis (7).

The regulation of emotions is closely linked to the hippocampus and parahippocampal gyrus (8), and these brain regions are also involved in cognitive functioning (9). Some studies have revealed abnormal brain activity in the hippocampus among BD patients and those at high risk of developing the disorder (10, 11). The hippocampus, a key component of the limbic system, is known to be involved in various cognitive functions, such as memory formation, consolidation, and retrieval (12). Alterations in hippocampal structure and function have been consistently observed in both depression and bipolar disorder, suggesting that these disorders may have shared underlying pathophysiology (13). The parahippocampal gyrus, which borders the hippocampus, is involved in sensory processing, attention, and spatial navigation. It also plays a role in the regulation of emotions and has been reported to exhibit changes in patients with mood disorders (14). Furthermore, a meta-analysis has reported functional and/or structural abnormalities in both the hippocampus and parahippocampal gyrus, suggesting that these regions are vulnerable in individuals with BD and may be responsible for early impairments in declarative memory (15). Therefore, investigating the hippocampus and parahippocampal gyrus in bipolar and unipolar depression may provide valuable insights into the underlying neural mechanisms associated with these conditions. By examining these regions, we can potentially identify biomarkers or diagnostic indicators that distinguish between these two major mood disorders, as well as understand the neural substrates of cognitive and affective symptoms. Thus, the choice of these specific brain regions for study is crucial in the pursuit of developing more targeted and effective treatments for bipolar and unipolar depression. Further depth in explaining the selection of the hippocampus and parahippocampal gyrus in research involving these disorders will enhance the understanding of their role in the pathophysiology and treatment of mood disorders.

In the last decades, functional magnetic resonance imaging (fMRI) has allowed to explore brain function both during the performance of a task and at rest. Particularly, resting-state fMRI has been widely used to analyze the differences in spontaneous brain activity and functional connectivity of various brain regions through various measures, including fractional Amplitude of Low-Frequency Fluctuations (fALFF) and Regional Homogeneity (ReHo) (16). The fALFF is a method for quantifying spontaneous brain activity by measuring the intensity fluctuation of fMRI signals with specific frequencies in a given region of interest (17). It reflects the

synchronization of neuronal oscillations within a region and has been used to investigate various neurological and psychiatric disorders (18). ReHo is another fMRI-based method for evaluating functional coherence within regions of interest. It measures the similarity of fMRI signal time series within a given region by calculating the correlation coefficient of fMRI signal fluctuations over specified periods of time (19). ReHo has been used to investigate cognitive processes, emotional regulation, and neurological disorders (20).

Given these findings, this study aims to investigate the diagnosis of bipolar and unipolar depression by integrating results from psychological assessments, fMRI scans, and cognitive evaluations. We hypothesize that functional abnormalities and cognitive differences in the hippocampus and parahippocampal gyrus can serve as distinguishing features between unipolar depression and bipolar depression. Therefore, we propose to examine data from the Hamilton Depression Rating Scale (HAMD), Hamilton Anxiety Rating Scale (HAMA), fMRI scans, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scores, and the ten cognitive domains of the RBANS scale. The aim of this study is to offer valuable perspectives for future studies on the diagnosis of bipolar depression and unipolar depressive disorders, contributing to a more comprehensive understanding of these conditions and informing more effective treatments.

Method

Participants

Participants (both MDD and BD groups) were recruited from the Third People's Hospital of Foshan. Patients were diagnosed according to the Structure interview of Diagnostic and Statistical Manual-5th edition (DSM-5). Notably, all BD patients were in a depressive phase (We used the 24-item HAMD for assessing depressive symptoms) (3). Healthy control (HC) participants were selected from local communities, matching the MDD and BD participants in terms of age, gender, education, and other relevant factors. Ethics Number: FSSY-LS202201.

Inclusion and exclusion criteria

Inclusion criteria for participants included being of Han nationality, right-handedness, having a first-episode drug-naïve mental illness, and no family history or underlying diseases. Diagnosis criteria for MDD or BD were based on the DSM-5. Exclusion criteria comprised contraindications to fMRI acquisition, the presence of brain organic or other physical diseases, substance abuse (including drugs and alcohol), traumatic brain injuries, and nervous system diseases, among others.

Scale assessment

Participants underwent assessment using the Hamilton Depression Rating Scale (HAMD), Hamilton Anxiety Rating Scale (HAMA), and RBANS scores. The HAMD questionnaire assessed the severity of the disease, while RBANS scores aimed at evaluating

cognitive function. The RBANS scale is a comprehensive neuropsychological assessment tool designed to evaluate a broad range of cognitive functions in adults (21). The scale consists of a series of standardized tests and tasks that aim to assess various cognitive domains, including attention, memory, language, executive functions, and visual-spatial abilities. These tasks are designed to be repeated and can be administered over multiple sessions to assess changes in cognitive performance over time. The scale provides quantitative scores that allow clinicians and researchers to compare an individual's cognitive performance to established norms based on age, education, and other relevant factors (22).

MRI acquisition

MRI acquisition was conducted using a General Electric 3T Excite HD scanner. The scan parameters were as follows: Time repetition (TR)/Echo time (TE)=8.6/3.3 ms, Flip angle (FA)=9°, Field of view (FOV)=256 mm * 256 mm, layer thickness=1 mm, slice number=172. For resting brain function MRI acquisition, parameters were TR/TE=2000/30 ms, FA=90°, FOV=240 mm * 240 mm, layer thickness=4 mm, number of layers=36, and layer spacing=1 mm.

Fractional amplitude of Low-frequency fluctuations analysis

The fALFF analysis was conducted following a previously established methodology (23). Essentially, the energy of each frequency within the low-frequency range ($0.01 \text{ Hz} < f < 0.1 \text{ Hz}$) was divided by the energy of each frequency across the entire frequency range to calculate the fALFF value for each voxel. This value was then normalized by dividing it by the average amplitude of the entire brain signal to account for overall level differences in fALFF.

Regional homogeneity analysis

ReHo analysis involved clustering twenty-seven voxels and applying the Kendall consistency coefficient (KCC) to measure the similarity between a voxel and its twenty-six neighboring voxels. The DPARSF software's standard brain model was used to obtain KCC maps for each subject. Subsequently, the KCC value for each voxel was normalized by dividing it by the average value from the standard brain model, resulting in standardized mean ReHo maps. These maps were then smoothed.

Data Preprocessing and processing

To ensure comprehensive assessments, all participants were requested to complete scale evaluations and fMRI data collection on the same day. Upon completion, fMRI images were visually examined to guarantee their quality and eliminate any unwanted artifacts or noise. Subsequently, the fMRI data was normalized to the MNI-152 template employing SPM8, and functional MRI data was registered to the structural fMRI using the registration tool in SPM8. To achieve

higher precision, the fMRI data was resampled to a resolution of 2 mm x 2 mm x 2 mm. To further enhance the data quality, fMRI data was smoothed using a Gaussian kernel with a full-width at half-maximum (FWHM) of 8 mm.

The data processing assistant for Resting-State fMRI (DPARSF), SPM8, and cat12 software were employed to preprocess the fMRI data. This included measuring the volume of the hippocampus and parahippocampal gyrus and analyzing the neural activity in these regions using fALFF and ReHo. Finally, the ReHo maps underwent spatial smoothing through the utilization of an 8 mm full-width at half maximum Gaussian kernel.

Statistical analyses

Statistical analyses were conducted using SPSS 24.00. The Kolmogorov-Smirnov test assessed the probability distribution of each group, and the results of all groups showed that they all obeyed normal distribution. The significance between groups was calculated by one-way analysis of variance (ANOVA) followed by a *post hoc* test, and all values are presented as means $\pm$ standard deviation (SD). Pearson correlation analysis was used to examine the relationships between hippocampal/parahippocampal gyrus volume and functional values and clinical data. Finally, *p*-values were corrected for multiple comparisons.

Results

Patient characteristics

A total of 165 participants were recruited for this study, including healthy controls ($n=46$), patients with MDD ($n=58$), and patients with BD ($n=61$). There were no significant differences in age, gender, body mass index (BMI), and years of education among the HC, MDD, and BD groups (Table 1). However, the BD group exhibited significantly lower scores in various cognitive domains, including immediate memory (learning and story memory), attention (coding and digit span), and delayed memory (list recognition, story recall, and figure recall), compared to the HC and MDD groups. Moreover, the BD group had lower attention (digit span) scores compared to the HC group. There were no significant differences in visuospatial construction and language among the HC, MDD, and BD groups (Table 2; Figure 1).

Hippocampus and Parahippocampal gyrus findings

In terms of volume, the right hippocampus volume was increased in the MDD group ($p < 0.001$), while in the BD group, it was decreased ($p < 0.01$) compared to the MDD group. However, there was no significant difference in right hippocampus volume between the HC and BD groups. In terms of functional measures, the BD group exhibited increased fALFF values in the hippocampus (left and right) compared to both the HC and MDD groups ($p < 0.01$). In addition, the BD group showed significantly increased regional homogeneity (ReHo) values in the hippocampus (left and right) and

TABLE 1 Description and comparison of Clinical Scales among Healthy Control, Major Depressive Disorder, and Bipolar Disorder Groups.

	HC	MDD	BD	Statistics
Participants	46	58	61	
Age (years)	32.20 ± 10.36	29.29 ± 12.44	30.05 ± 9.11	$F = 0.136; p = 0.375$
Gender (M/F)	19/27	23/35	23/38	$\chi^2 = 0.241; p = 0.969$
BMI	22.24 ± 3.43	22.23 ± 3.85	23.29 ± 3.76	$F = 0.220; p = 0.217$
Education				
Below 9 years, n	14	15	19	$\chi^2 = 0.293; p = 0.864$
9 years and above, n	32	43	42	
HAMD score	2.5 ± 3.67	23.53 ± 7.40**	14.07 ± 9.29***	$F = 102.3; P^{**} < 0.001, P^{*} < 0.001$
HAMA score	2.02 ± 2.59	16.04 ± 5.53**	9.87 ± 7.43***	$F = 74.3; P^{**} < 0.001, P^{*} < 0.001$
RBANS	190.2 ± 39.50	181.2 ± 35.58	156.8 ± 33.14***	$F = 12.84; P^{**} < 0.001, P^{*} < 0.001$
Immediate memory (Learning)	27.63 ± 7.03	26.22 ± 6.49	21.89 ± 6.36***	$F = 11.45; P^{**} < 0.001, P^{*} < 0.001$
Immediate memory (Story Memory)	14.41 ± 5.96	13.05 ± 5.66	9.41 ± 4.66***	$F = 12.70; P^{**} < 0.001, P^{*} < 0.001$
Visuospatial Construction	17.76 ± 2.41	18.47 ± 2.38	17.31 ± 3.32	$F = 2.602; p = 0.077$
Language	18.28 ± 4.34	17.36 ± 4.70	16.52 ± 4.44	$F = 2.00; p = 0.139$
Attention (Digit span)	14.13 ± 2.18	13.52 ± 2.68	12.75 ± 5.54*	$F = 4.069; P^{*} = 0.015$
Attention (Coding)	49.80 ± 14.15	46.57 ± 13.20	40.43 ± 13.46***	$F = 6.721; P^{**} = 0.002, P^{*} = 0.039$
Delayed memory (List Recall)	6.61 ± 3.11	5.88 ± 2.94	4.66 ± 2.53**	$F = 6.523; P^{**} = 0.002$
Delayed memory (List Recognition)	19.54 ± 1.05	19.38 ± 1.18	18.64 ± 1.73**	$F = 6.833; P^{**} = 0.003, P^{*} = 0.011$
Delayed memory (Story Recall)	7.52 ± 3.74	7.14 ± 3.70	4.46 ± 2.98***	$F = 13.17; P^{**} < 0.001, P^{*} < 0.001$
Delayed memory (Figure Recall)	14.46 ± 4.71	13.59 ± 4.26	10.70 ± 4.97**	$F = 9.908; P^{**} < 0.001, P^{*} = 0.003$

HC: healthy control; MDD: major depressive disorder; BD: bipolar disorder; BMI: Body Mass Index; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; * $p < 0.05$, ** $p < 0.01$ compared to HC group; # $p < 0.05$, ## $p < 0.01$ compared to MDD group.

TABLE 2 Comparison of MRI data among HC, MDD and BD.

	HC	MDD	BD
Volume (cm ³)			
Hippocampus (Left)	3.69 ± 0.36	3.69 ± 0.36	3.70 ± 0.31
Hippocampus (Right)	3.62 ± 0.35	3.88 ± 0.34**	3.61 ± 0.30#
Parahippocampal gyrus (Left)	3.46 ± 0.31	3.37 ± 0.31	3.48 ± 0.32
Parahippocampal gyrus (Right)	4.04 ± 0.42	3.89 ± 0.39	4.00 ± 0.39
FALFF (a.u.)			
Hippocampus (Left)	−0.64 ± 0.17	−0.66 ± 0.15	−0.57 ± 0.16**
Hippocampus (Right)	−0.63 ± 0.16	−0.61 ± 0.18	−0.50 ± 0.17***
Parahippocampal gyrus (Left)	−0.52 ± 0.25	−0.47 ± 0.23	−0.45 ± 0.24
Parahippocampal gyrus (Right)	−0.51 ± 0.21	−0.47 ± 0.21	−0.42 ± 0.22
ReHo (a.u.)			
Hippocampus (Left)	−0.81 ± 0.19	−0.88 ± 0.14	−0.75 ± 0.15**
Hippocampus (Right)	−0.88 ± 0.17	−0.85 ± 0.15	−0.75 ± 0.16***
Parahippocampal gyrus (Left)	−0.56 ± 0.18	−0.61 ± 0.18	−0.50 ± 0.20**
Parahippocampal gyrus (Right)	−0.61 ± 0.17	−0.66 ± 0.20	−0.54 ± 0.18**

HC: healthy control; MDD: major depressive disorder; BD: bipolar disorder; FALFF: fractional amplitude of low frequency fluctuation; ReHo: regional homogeneity; The fALFF and ReHo values were measured in normalized unit arbitrary unit (a.u.). * $p < 0.05$, ** $p < 0.01$ compared to HC group; # $p < 0.05$, ## $p < 0.01$ compared to MDD group.

parahippocampal gyrus (left and right) compared to the HC group ($p < 0.01$). Moreover, the BD group demonstrated significantly higher ReHo values in the right hippocampus compared to the MDD group ($p < 0.01$).

Pearson correlation analysis

The results of Pearson correlation analysis revealed several significant associations (Table 3). Specifically, the ReHo values in

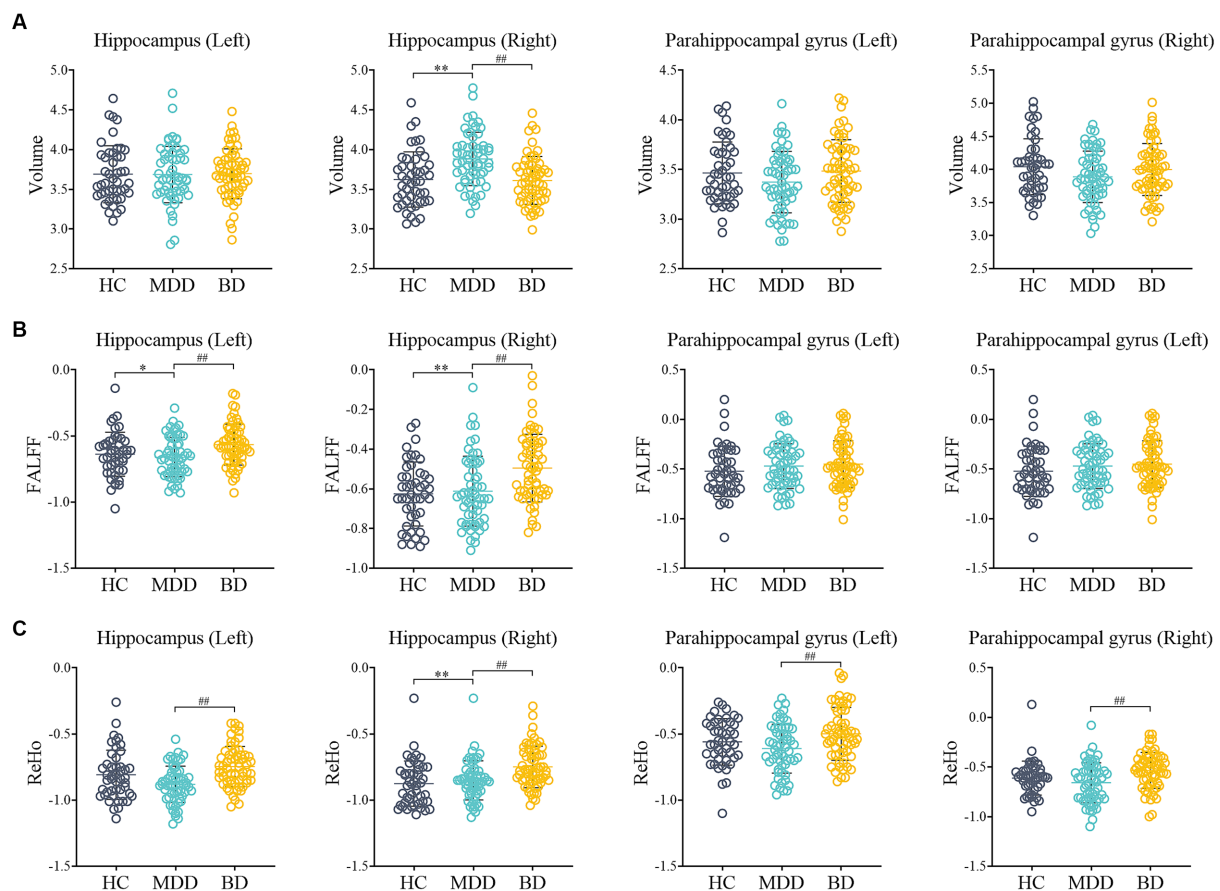


FIGURE 1

Comparison of MRI data among HC, MDD and BD. **(A)** The volume of Hippocampus (Left, Right) and Parahippocampal gyrus (Left, Right); **(B)** The fALFF of Hippocampus (Left, Right) and Parahippocampal gyrus (Left, Right); **(C)** The ReHo of Hippocampus (Left, Right) and Parahippocampal gyrus (Left, Right); HC: healthy control; MDD: major depressive disorder; BD: bipolar disorder; fALFF: fractional amplitude of low frequency fluctuation; ReHo: regional homogeneity; * $p < 0.05$, ** $p < 0.01$ compared to HC group; # $p < 0.05$, ## $p < 0.01$ compared to MDD group.

the right hippocampus were positively correlated with HAMD scores ($r = 0.32$, $p = 0.046$) and HAMA scores ($r = 0.27$, $p = 0.04$). However, there were no significant correlations found between the volume, fALFF, and ReHo of the hippocampus (left and right) and parahippocampal gyrus (left and right) with total RBANS scores.

Moreover, the volume of the left parahippocampal gyrus exhibited negative correlations with immediate memory (learning) ($r = -0.25$, $p = 0.037$), language ($r = -0.29$, $p = 0.02$), and attention (coding) ($r = -0.32$, $p = 0.03$). On the other hand, the volume of the right parahippocampal gyrus showed a positive correlation with visuospatial construction ($r = 0.29$, $p = 0.04$).

In terms of functional measures, the fALFF value of the right hippocampus was positively correlated with immediate memory (story memory) ($r = 0.27$, $p = 0.035$) and delayed memory (story recall) ($r = 0.27$, $p = 0.03$). Additionally, the ReHo value of the left hippocampus was found to have negative correlations with delayed memory (list recall) ($r = -0.34$, $p = 0.03$) and delayed memory (list recognition) ($r = -0.41$, $p = 0.02$). Lastly, the ReHo value of the left parahippocampal gyrus exhibited a positive correlation with immediate memory (learning) ($r = 0.32$, $p = 0.04$). Further analysis with Bonferroni correction showed that there was no significance

among the volume, fALFF, and ReHo of the hippocampus (left and right) and parahippocampal gyrus (left and right).

Discussion

This study utilizes rsMRI technology and automatic segmentation tools to unveil insights into the gray matter volume and brain function indicators of the hippocampus and parahippocampal gyrus in individuals with Bipolar Disorder (BD). Additionally, we conducted correlation analyses with the severity of the disorder and cognitive function. Our findings underscore that cognitive impairment in Bipolar Depression is significantly more pronounced when compared to both Healthy Controls (HC) and Major Depressive Disorder (MDD) patients. Moreover, we established a strong connection between specific functions of the hippocampus, parahippocampal gyrus, cognitive function, and disease severity.

Cognitive dysfunction has consistently emerged as a prominent feature in both MDD and BD (24). This impairment is intricately linked to overall functional outcomes and plays a crucial role in disease prognosis (25). Previous reports have indicated that BD patients exhibit more severe cognitive deficits compared to MDD

TABLE 3 Pearson correlation analysis of the indicators in the hippocampus and parahippocampal gyrus with the severity of BD and cognitive function.

		Volume				FALFF				ReHo			
		Hippocampus (Left)	Hippocampus (Right)	Parahippocampal gyrus (Left)	Parahippocampal gyrus (Right)	Hippocampus (Left)	Hippocampus (Right)	Parahippocampal gyrus (Left)	Parahippocampal gyrus (Right)	Hippocampus (Left)	Hippocampus (Right)	Parahippocampal gyrus (Left)	Parahippocampal gyrus (Right)
HAMD	r	−0.03	0.02	−0.002	0.04	0.06	0.02	0.03	0.04	−0.08	0.32	−0.09	−0.01
	P	0.84	0.87	0.99	0.76	0.63	0.88	0.85	0.78	0.53	0.046*	0.49	0.92
HAMA	r	−0.04	−0.03	−0.02	0.005	0.08	0.004	0.1	0.06	−0.08	0.27	−0.13	0.008
	P	0.78	0.85	0.9	0.97	0.54	0.98	0.44	0.66	0.56	0.04*	0.34	0.95
RBNAS	r	−0.03	−0.004	−0.17	−0.08	−0.14	0.09	0.02	0.06	−0.19	−0.01	0.08	−0.005
	P	0.8	0.98	0.19	0.53	0.27	0.48	0.88	0.66	0.14	0.93	0.54	0.97
Immediate memory (Learning)	r	−0.1	−0.009	−0.25	−0.17	−0.11	0.09	0.12	0.19	−0.12	0.03	0.32	0.08
	P	0.45	0.95	0.037*	0.2	0.41	0.51	0.34	0.15	0.36	0.8	0.04*	0.53
Immediate memory (Story Memory)	r	0.02	0.009	0.04	0.02	−0.04	0.27	0.02	0.018	−0.22	0.19	−0.04	−0.03
	P	0.86	0.95	0.74	0.86	0.77	0.035*	0.87	0.89	0.086	0.15	0.74	0.81
Visuospatial Construction	r	0.19	0.18	0.19	0.29	−0.22	−0.1	0.003	−0.08	−0.18	−0.02	−0.02	0.05
	P	0.14	0.17	0.14	0.04*	0.09	0.44	0.98	0.52	0.16	0.85	0.89	0.68
Language	r	−0.11	−0.12	−0.29	−0.18	−0.03	0.17	0.06	0.17	−0.04	0.01	−0.01	−0.06
	P	0.42	0.36	0.02*	0.17	0.8	0.19	0.65	0.19	0.74	0.93	0.92	0.65
Attention (Digit Span)	r	0.17	0.16	0.1	0.16	−0.16	−0.04	−0.06	−0.1	−0.17	0.03	0.03	−0.05
	P	0.2	0.2	0.46	0.23	0.22	0.75	0.63	0.47	0.2	0.84	0.79	0.71
Attention (Coding)	r	−0.08	−0.05	−0.32	−0.13	−0.11	−0.03	−0.07	−0.004	−0.09	−0.12	0.09	0.01
	P	0.57	0.68	0.03*	0.31	0.38	0.81	0.6	0.97	0.5	0.36	0.47	0.92
Delayed memory (List Recall)	r	0.03	−0.03	−0.07	−0.06	−0.18	0.05	0.14	0.08	−0.34	0.01	0.01	−0.09

(Continued)

TABLE 3 (Continued)

		Volume				FALFF				ReHo			
		Hippocampus (Left)	Hippocampus (Right)	Parahippocampal gyrus (Left)	Parahippocampal gyrus (Right)	Hippocampus (Left)	Hippocampus (Right)	Parahippocampal gyrus (Left)	Parahippocampal gyrus (Right)	Hippocampus (Left)	Hippocampus (Right)	Parahippocampal gyrus (Left)	Parahippocampal gyrus (Right)
	P	0.82	0.84	0.6	0.65	0.18	0.69	0.27	0.53	0.03*	0.91	0.91	0.5
Delayed memory (List Recognition)	r	−0.11	−0.08	−0.14	−0.07	0.05	0.11	0.12	0.13	−0.41	−0.07	0.002	−0.05
	P	0.39	0.55	0.28	0.62	0.7	0.4	0.36	0.32	0.02*	0.58	0.99	0.72
Delayed memory (Story Recall)	r	−0.04	−0.02	−0.11	−0.09	−0.04	0.27	−0.01	0.03	−0.09	0.15	−0.01	−0.09
	P	0.79	0.9	0.38	0.51	0.78	0.03*	0.93	0.83	0.5	0.24	0.93	0.5
Delayed memory (Figure Recall)	r	0.02	0.08	−0.03	0.02	−0.12	0.05	0.007	−0.02	−0.17	−0.05	0.04	0.02
	P	0.88	0.54	0.81	0.86	0.35	0.73	0.96	0.88	0.2	0.71	0.74	0.89

HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

patients (26). Our study confirms these observations, demonstrating that BD patients experience more pronounced cognitive dysfunction than HC and MDD groups. Specifically, the BD group displayed significant disparities in immediate memory, attention, and delayed memory when compared to the HC group, aligning with earlier research (27). It's important to note that there were no significant cognitive impairments detected in any of the MDD groups, potentially attributed to the relatively small sample size of MDD patients.

MRI studies in the context of psychiatric disorders have consistently reported abnormal hippocampal volumes, influenced by various factors (28). Some studies suggest that structural changes in the hippocampus are state-dependent, occurring during acute phases of MDD and returning to normal after remission (29). Conversely, exercise has been associated with increased hippocampal volume (30). Our study reveals a significant increase in the right hippocampal volume of MDD patients, while no significant differences were observed in the BD group compared to the HC group. This suggests that factors such as age, medication, exercise, and others may exert influence on hippocampal volume (30).

Previous research has noted abnormal brain activity in BD patients, closely linked to their cognitive function, potentially serving as a means to differentiate BD from MDD patients (31). Significant differences were observed in brain regions encompassing the ventral and dorsolateral prefrontal cortex, insula, and putamen (32). However, there have been limited studies examining the global neural activity characteristics of the hippocampus and parahippocampal gyrus in BD and MDD patients using fALFF and ReHo values. In our study, we compared fALFF and ReHo, which provide insights into the strength and synchronization of local neural signals in the hippocampus and parahippocampal gyrus. Our results indicated that BD patients exhibited enhanced neural activity in the hippocampus (both left and right) compared to the HC and MDD groups. Furthermore, in terms of synchronization, both the hippocampus (left and right) and parahippocampal gyrus (left and right) showed elevated ReHo in BD patients when compared to the HC and MDD groups. These findings align with functional imaging studies that have highlighted abnormal brain activation in the hippocampus and parahippocampal gyrus during attention, emotional, and memory-related tasks. This consistency with neuropsychological findings, which reveal cognitive impairments during acute emotional episodes and significant declarative memory impairment during remission (33, 34), suggests that abnormal activity in the hippocampus and parahippocampal gyrus, as cognitive control regions, could potentially serve as biomarkers for distinguishing between BD and MDD.

In our study, we conducted Pearson correlation analyses between hippocampal and parahippocampal gyrus volumes, fALFF, ReHo, and cognitive function in BD patients. Interestingly, we found that the volumes of the hippocampus and parahippocampal gyrus showed no significant differences concerning HAMD, HAMA, and RBANS scores, contradicting some previous findings (14, 35). This discrepancy may be attributed to the specific characteristics of our study participants, who exhibited a relatively short course of BD with no functional abnormalities during the MRI process (36, 37). Regarding cognitive processes, previous research has emphasized the centrality of the hippocampus (38, 39). Our results supported this notion by revealing the involvement of the hippocampus in memory and attention functions. Additionally, we found a positive correlation between fALFF values in the hippocampus and parahippocampal

gyrus and immediate and delayed memory, consistent with previous studies (40, 41). Furthermore, our study explored the less-studied Pearson correlation between hippocampal ReHo values and depressive scores, revealing a positive correlation between hippocampal ReHo values and HAMD and HAMA scores.

Nonetheless, several limitations warrant consideration in our study. One limitation of the present study is the lack of assessment regarding potential protective factors through psychotherapy and counseling intervention. Although individuals often utilize these non-pharmacological treatments without prescription to prevent or alleviate symptoms at the onset of mental illness (42), such information was not collected or analyzed in our study. Consequently, the potential influence of these protective factors on the observed MRI abnormalities remains unknown. Future research should consider incorporating measures of psychotherapy and counseling intervention to provide a more comprehensive understanding of their potential impact on functional and structural MRI abnormalities in bipolar and unipolar depression. Secondly, the uncontrolled effects of medications, despite general alignment with prior research, remain a limitation. Although the patients were drug-naïve, they may have been prescribed medications or other medical conditions. Additionally, the MDD patients included in our study exhibited a younger onset age compared to BD patients, which represents an atypical feature of depressive episodes and is considered a risk factor for BD (43). Lastly, our relatively small sample size, while comparable to previous studies, may limit the generalizability of our findings (44). Future research should endeavor to combine clinical phenotypes and employ longitudinal methods to replicate our results and provide more conclusive evidence.

Conclusion

In conclusion, our study reveals distinctive intrinsic activity patterns in the hippocampus and parahippocampal gyrus of BD patients when compared to MDD and HC patients. These patterns may signify different underlying pathophysiological mechanisms in BD. Changes in fALFF and ReHo observed in the hippocampus and parahippocampal gyrus between BD and MDD patients are strongly associated with cognitive functions. Furthermore, the notable abnormal spontaneous neural activity detected in these regions may serve as a potential neural basis for distinguishing between bipolar depression and unipolar depression. Consequently, abnormal intrinsic brain activity opens up a new avenue for future research, shedding light on neuroimaging-based biomarkers for differentiating bipolar depression from unipolar depression.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the ethics committee of the Third People's Hospital of Foshan, China.

The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SH: Data curation, Writing – original draft. XW: Data curation, Writing – original draft. ZL: Data curation, Methodology, Writing – original draft. CL: Formal analysis, Methodology, Writing – original draft. YH: Formal analysis, Methodology, Writing – original draft. JL: Data curation, Writing – review & editing. WH: Funding acquisition, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Enhancing generalized anxiety disorder diagnosis precision: MSTCNN model utilizing high-frequency EEG signals

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Generalized Anxiety Disorder (GAD) is a prevalent mental disorder on the rise in modern society. It is crucial to achieve precise diagnosis of GAD for improving the treatments and averting exacerbation. Although a growing number of researchers beginning to explore the deep learning algorithms for detecting mental disorders, there is a dearth of reports concerning precise GAD diagnosis. This study proposes a multi-scale spatial-temporal local sequential and global parallel convolutional model, named MSTCNN, which designed to achieve highly accurate GAD diagnosis using high-frequency electroencephalogram (EEG) signals. To this end, 10-min resting EEG data were collected from 45 GAD patients and 36 healthy controls (HC). Various frequency bands were extracted from the EEG data as the inputs of the MSTCNN. The results demonstrate that the proposed MSTCNN, combined with the attention mechanism of Squeeze-and-Excitation Networks, achieves outstanding classification performance for GAD detection, with an accuracy of 99.48% within the 4–30Hz EEG data, which is competitively related to state-of-art methods in terms of GAD classification. Furthermore, our research unveils an intriguing revelation regarding the pivotal role of high-frequency band in GAD diagnosis. As the frequency band increases, diagnostic accuracy improves. Notably, high-frequency EEG data ranging from 10–30 Hz exhibited an accuracy rate of 99.47%, paralleling the performance of the broader 4–30Hz band. In summary, these findings move a step forward towards the practical application of automatic diagnosis of GAD and provide basic theory and technical support for the development of future clinical diagnosis system.

KEYWORDS

generalized anxiety disorder (GAD), electroencephalogram (EEG), convolutional neural network (CNN), attention mechanisms, deep learning

1 Introduction

Generalized Anxiety Disorder (GAD) is a common psychiatric disorder characterized by persistent anxiety, irritability, sleep disturbances, and nervousness (1). In addition, patients with GAD often have physical symptoms such as palpitations, dry mouth, and excessive sweating (2). Recently, the incidence of GAD has significantly increased and has

become a global health issue. It is reported that the global rate of the people with anxiety disorder was 26% in 2020, and the growth rate has accelerated compared to previous years (3). The lifetime prevalence rate of GAD in the general population is as high as 5% (4). Females have a much higher probability of developing this disorder compared to males (5). GAD not only brings negative impacts on the psychological and physical health of patients but also has the potential to seriously affect their daily functioning, social interaction, and quality of life.

The etiological factor of GAD is exceedingly intricate, encompassing the interplay of genetic, biological, and psychosocial factors (6, 7). The complex etiologies of GAD emphasize the need for a targeted treatment approach. Therefore, timeous diagnosis combined with effective treatment is crucial to avoid GAD becoming more severe and harder to treat (8). Currently, clinical diagnosis of GAD mainly relies on clinical assessment and subjective scales (9). These methods are highly subjective and rely heavily on accurate diagnosis by the psychiatrists and accurate self-reporting by the patients, which may easily lead to inconsistency and inaccuracy in diagnosis and assessing efficacy. Therefore, it is crucial to seek objective and precise diagnostic methods for GAD.

With the continuous developments of psychiatric neuroscience, a range of neuroimaging techniques have been applied to the study of psychiatric diseases including electroencephalogram (EEG) (10, 11), magnetoencephalography (MEG) (12), near-infrared spectroscopy (NIRS) (13), and functional magnetic resonance imaging (fMRI) (14). Among these techniques, EEG has excellent timing resolution and high time sensitivity, while being non-invasive and simple to operate (15, 16). EEG can record and measure the brain activity, offering valuable insights into its dynamic functioning (17). In recent years, the application of EEG to GAD has been continuously explored to help uncover the complex neuro-electrophysiological mechanism and provide more effective detection methods. Previous studies have utilized EEG to observe changes in the brain of GAD patients, such as increased brain activity (18) and alterations in brain network structure (19). Furthermore, by extracting various types of EEG features, such as functional connectivity (19), power spectral density (20), and correlation dimension (21), researchers found significant differences in features between GAD patients and healthy controls. Until now, EEG has been widely used to assist in the diagnosis of various psychiatric disorders, such as anxiety (22, 23), depression (24, 25), obsessive-compulsive disorder (26, 27), Alzheimer's (28, 29), schizophrenia (30, 31). These studies imply that EEG is a valuable and promising neuroimaging technique in the diagnosis of GAD.

Prior research related to mental disorder detection that combines artificial intelligence and EEG can be mainly divided into two categories. On the one hand, some researchers extract diverse EEG features (32–34), utilizing machine learning models for classification. This strategy strongly relies on the classification performances of the extracted features and the adaptability of the machine learning models. On the other hand, existence of researchers building deep learning models and using EEG signals as the inputs for classification. Deep learning can overcome the shortcomings of high feature dependence and limited shallow models. It streamlines processing by enabling automated end-to-end learning, integrating feature extraction and classification. Deep learning has demonstrated significant success in the processing of complex data (35). Due to the excellent end-to-end learning and ability to effectively utilize data

hierarchies, convolutional neural network (CNN) has emerged as a widely favored architecture in deep learning-EEG research (36). For instance, Abdulhakim employed three different deep learning models: CNN, long short term memory (LSTM), CNN + LSTM, and achieved the highest accuracy of 92.86% for social anxiety disorder identification with CNN + LSTM model (37). Although the combination of EEG and deep learning has shown remarkable success in variety of fields (38–40), according to our previous survey, it is rarely utilized in GAD diagnosis, which highlights the urgent need for enhanced diagnostic methods in this specific domain.

Given the challenging low signal-to-noise ratio of EEG signals and complex spatiotemporal dynamic patterns, the importance of feature extraction in deep learning is magnified. As an efficient and rapid EEG signal feature extraction tool, CNN plays a powerful role in the field of EEG signal analysis. For EEG signals, traditional time-frequency domain feature extraction methods encounter challenges to fully capture the intricate details. Consequently, adopting the spatial-temporal joint feature extraction method has a stronger signal representation ability in CNN model (41). Moreover, multi-scale convolution of CNN has been emphasized in EEG feature extraction. This technique can capture different levels of features at different scales, thereby enhancing the characterization ability of the model. Researchers have successfully applied multi-scale convolution to feature extraction, yielding favorable outcomes (42–44). For instance, Wu et al. introduced a parallel multi-scale filter bank CNN for EEG classification, and achieved excellent classification performance (44). To further elevate CNN performance, multi-scale convolution was introduced into the spatial-temporal feature extraction for GAD diagnosis.

In this study, we propose an end-to-end deep learning model architecture called MSTCNN based on multi-scale spatial-temporal convolution to facilitate in the precise diagnosis of GAD. To ensure the effectiveness of MSTCNN, we conducted a sequence of ablation experiments to validate the efficacy of our selection strategy in model design. In addition, we try to use MSTCNN to reveal the key frequency bands of GAD, which helps us understand the potential differences of GAD in different frequency bands of EEG signals. Our research strives to present a viable approach for the precise diagnosis of GAD.

2 Materials and methods

2.1 Subjects

A total of 45 patients with GAD (13 males, 32 females, age: 22–55 years, 41.8 ± 9.4 years) and 36 healthy controls (HC) (11 males, 25 females, age: 21–57 years, 36.9 ± 11.3 years) were enrolled in this study, and there was no statistically significant difference in age between GAD and HC. All patients were diagnosed by the specialized psychiatrists and meet the DSM-5-TR criteria for GAD diagnosis. And all subjects should complete the questionnaire of Hamilton Anxiety Rating Scale (HAMA) and meet the following criteria: HAMA scores ≥ 14 for GAD; HAMA scores ≤ 7 for HC. Additionally, GAD patients had no other comorbidities (such as depression and other disorders). The average HAMA score in the GAD group was 27.1 ± 9.0 , and in the HC group was 2.3 ± 0.9 . Moreover, each participant was required to meet stringent EEG data collection

requirements: (1) no other psychiatric disorders and brain damage; (2) right-handed; (3) no drug and alcohol abuse; (4) not stay up late the day before the EEG data collection; (5) no smoking, coffee and strong tea before eight hours of EEG data collection. The entire experiment received approval from the Ethics Committee of Zhejiang Normal University, and all participants provided a written informed consent form before the experiment.

2.2 EEG data collection and preprocessing

Participants were asked to close eyes, stay awake and stationary, and reduce head and body movements and eye movements to reduce interference from ocular and electromyography. Every participant would record clinical resting EEG for 10 min. The EEG acquisition device is Nicolet EEG TS215605. Following the international 10–20 system, 16 electrodes were chosen, namely Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, and P8. The reference electrode refers to the left and right mastoid electrodes. The sampling frequency is 250 Hz, and the impedance of each electrode is controlled below 5k Ω . The whole experiment took place within the professional EEG laboratory of the local hospital.

Then, the EEGLAB embedded in MATLAB R2021a was used to preprocess EEG. Firstly, the original EEG signal was down-sampled

from 250 Hz to 125 Hz, and the signal was filtered by 4–30 Hz bandpass using a 4-order Butterworth filter. Secondly, fast independent component analysis (ICA) was used to remove EEG artifacts. Then, 4 s of continuous EEG signals were extracted as an EEG sample, resulting in a total of 5,371 samples for GAD and 4,018 samples for HC. Finally, the same bandpass filter was used to divide the EEG signal into five basic bands: Theta (4–8 Hz), Alpha1 (8–10 Hz), Alpha2 (10–13 Hz), Beta1 (13–20 Hz), Beta2 (20–30 Hz), and three extended bands: 13–30 Hz, 10–30 Hz, 8–30 Hz.

2.3 MSTCNN model

In this study, we proposed an innovative deep learning model named MSTCNN for GAD detection, which incorporates multi-scale spatial-temporal local sequential and global parallel convolutions. This architecture is further enhanced through the integration of an attention mechanism strategy. Its basic flow is shown in Figure 1. Detailed parameters of MSTCNN can be found in Table 1. The framework of MSTCNN can be divided into a feature extraction layer and a feature classification layer. (1) The feature extraction layer aims to learn and extract the most representative features from the original EEG signal, capturing the crucial information of the input data to provide support for subsequent classification tasks. This layer includes

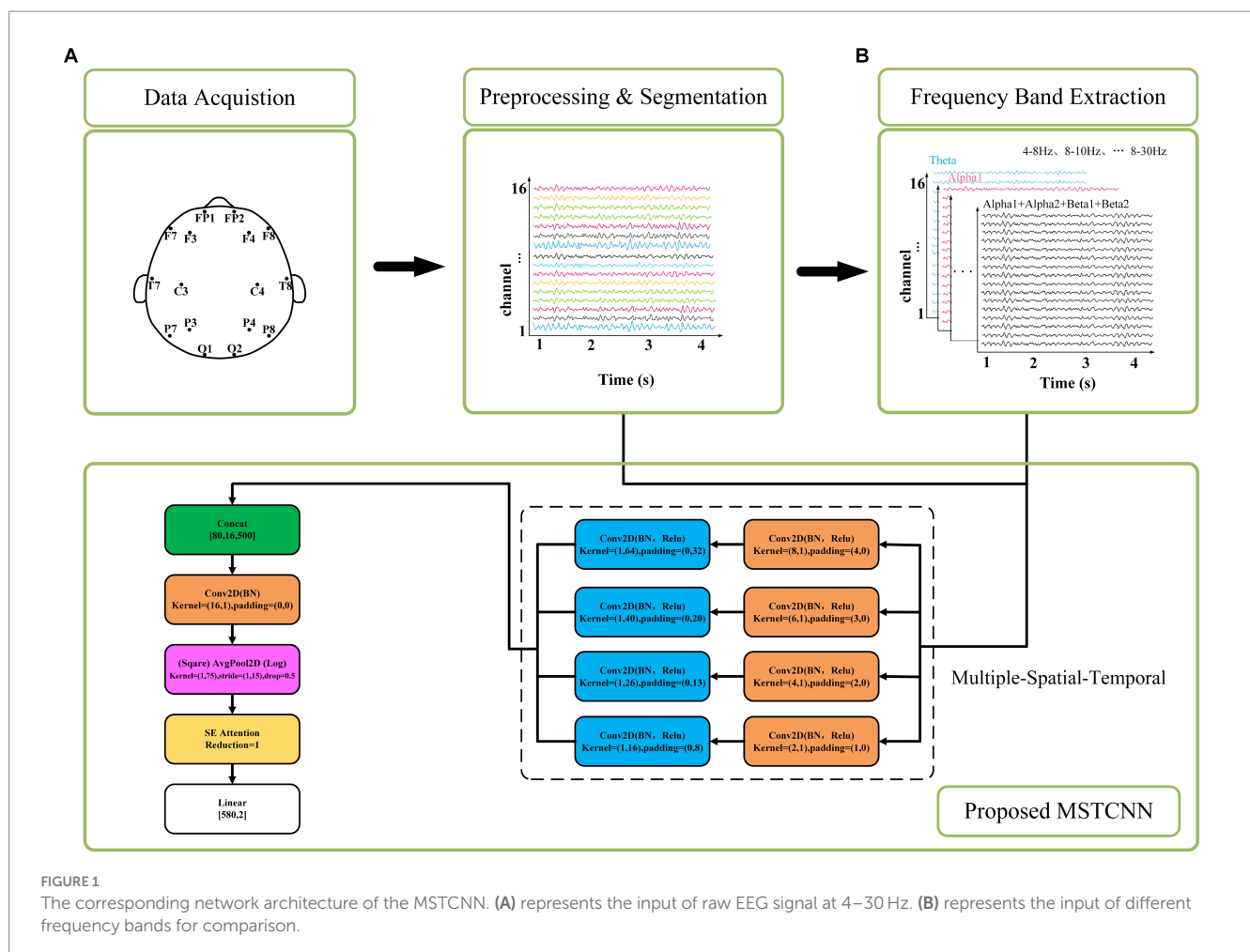


FIGURE 1

The corresponding network architecture of the MSTCNN. (A) represents the input of raw EEG signal at 4–30 Hz. (B) represents the input of different frequency bands for comparison.

TABLE 1 Parameters of proposed MSTCNN architecture.

Layer	Filters	Size	Stride	Output	Padding
Input				(16, 500)	
Reshape				(1, 16, 500)	
SpaConv1	10	(8, 1)	(1, 1)	(10, 16, 500)	Same
BatchNorm (ReLU)				(10, 16, 500)	
TemConv1	20	(1, 64)	(1, 1)	(20, 16, 500)	Same
BatchNorm (ReLU)				(20, 16, 500)	
SpaConv2	10	(6, 1)	(1, 1)	(10, 16, 500)	Same
BatchNorm (ReLU)				(10, 16, 500)	
TemConv2	20	(1, 40)	(1, 1)	(20, 16, 500)	Same
BatchNorm (ReLU)				(20, 16, 500)	
SpaConv3	10	(4, 1)	(1, 1)	(10, 16, 500)	Same
BatchNorm (ReLU)				(10, 16, 500)	
TemConv3	20	(1, 26)	(1, 1)	(20, 16, 500)	Same
BatchNorm (ReLU)				(20, 16, 500)	
SpaConv4	10	(2, 1)	(1, 1)	(10, 16, 500)	Same
BatchNorm (ReLU)				(10, 16, 500)	
TemConv4	20	(1, 16)	(1, 1)	(20, 16, 500)	Same
BatchNorm (ReLU)				(20, 16, 500)	
Concat				(80, 16, 500)	
SpaConv5	20	(16, 1)	(1, 1)	(20, 1, 500)	0
BatchNorm				(20, 1, 500)	
Square				(20, 1, 500)	
AveragePool		(1, 75)	(1, 15)	(20, 1, 29)	0
Log				(20, 1, 29)	
Dropout				(20, 1, 29)	
Attention				(20, 1, 29)	
Flatten				580	
Classifier	580			2	

spatiotemporal feature extraction, spatial feature extraction, and attention mechanism modules. The spatiotemporal feature extraction layer adopts multi-scale convolution, which helps to effectively extract spatiotemporal features at different scales. The spatial feature extraction layer is used to extract spatial features and reduce the dimensionality of the data. Prior to being fed into the fully connected layer, attention mechanism modules are added to enhance attention to important features and further improve model performance. (2) The feature classification layer primarily consists of nonlinear function, Dropout and pooling layer, which is used to enhance the nonlinear expressive ability, mitigate overfitting risks, and reduce data dimensionality.

2.3.1 Feature extraction layer

Here, the multi-scale spatial and temporal feature extraction convolutions are combined to maximize the utilization of the spatiotemporal information in the EEG data. As shown in Figure 2, In order to obtain the best feature extraction layer structure, numerous ablation experiments, including five feature extraction modules within the multi-scale convolution structure, were designed to validate the

efficacy of our proposed model for comparison. We conducted in-depth analysis on the spatiotemporal feature extraction module, and tried different combinations based on temporal convolution (44). In addition, batch normalization is introduced to enhance the consistency and stability of the model between different samples, and ReLU activation function is used to help the model better learn nonlinear features and improve the expression ability of the model. With these improvements, we expected to improve the performance and robustness of the model.

2.3.1.1 Convolution + batch normalization + ReLU structure

Convolution + batch normalization + ReLU is a common feature extraction combination in deep learning, and has been successfully applied in some popular frameworks. The batch normalization layer speeds up the convergence of the network by normalizing each mini-batch. It reduces the internal covariance movement of each layer of input data and fixes its range to a smaller range, which helps the network learn effective feature representations faster. ReLU introduces a nonlinear activation function in the network, which does not cause

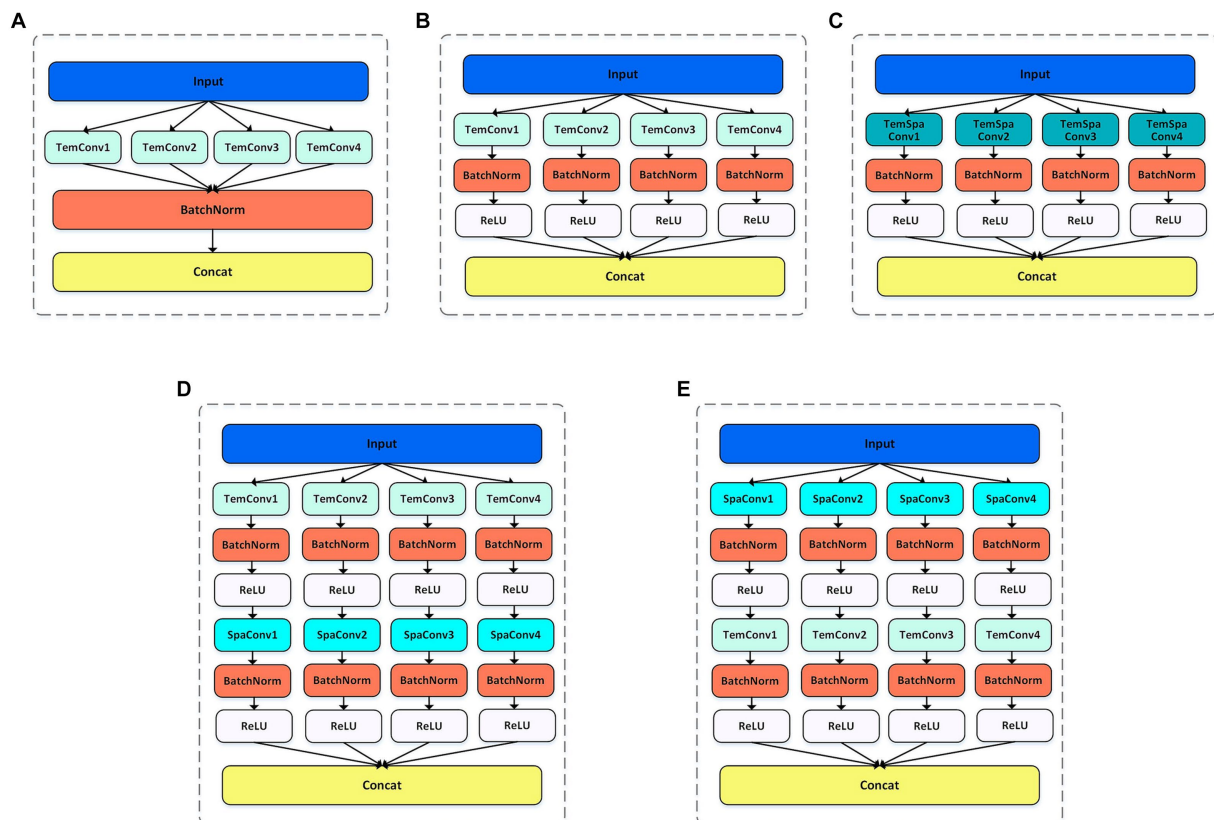


FIGURE 2

Five feature extraction structures. BR means adding BatchNorm and ReLU functions after the convolution. **(A)** TemConv: Temporal convolution. **(B)** TemConv+BR: temporal convolution followed by BR. **(C)** TemSpaConv+BR: temporal convolution and spatial convolution share a same convolution kernel and combined with BR. **(D)** TemConv+SpaConv+BR: temporal convolution followed by the spatial convolution and combined with BR. **(E)** SpaConv+TemConv+BR: spatial convolution followed by the temporal convolution and combined with BR.

gradient vanishing problems and can propagate gradients better than traditional activation functions such as sigmoid and tanh. The combined structure of Convolution + batch normalization + ReLU can accelerate convergence, improve generalization, mitigate gradient vanishing problems, and amplify the network's expressiveness. Through the incorporation of batch normalization and ReLU modules after temporal convolution (Figure 2A), the model becomes more robust and has stronger feature extraction capabilities, as shown in Figure 2B.

2.3.1.2 Spatial–temporal convolution

Temporal convolution can capture the temporal characteristics of the temporal evolution information, and the spatial convolution can capture the spatial characteristics between different channels. There are complex dynamic interactions between different brain regions in EEG signals, and spatiotemporal convolution can more effectively capture the dynamic connections and interactions between different channels in EEG signals than relying solely on temporal convolution. When the input is Channel $\times$ Time, a single convolution is employed to extract spatiotemporal features, only so that the kernel size is greater than 1 in both the temporal dimension and spatial dimension of the extracted features (i.e., $C > 1$ & $T > 1$, where C represents the kernel size of the spatial dimension and T represents the kernel size of the temporal dimension). Here, we referred to the Inception structure

(multiple kernels of different sizes are used in the space–time dimension to capture features at different scales and levels of abstraction) as shown in Figure 2C. However, the results of spatiotemporal feature extraction using a single convolution prove to be suboptimal. In order to improve spatiotemporal feature extraction, we explored how to add spatiotemporal convolution to the model to obtain better results. Inspired by the idea of SqueezeNeXt model that decomposing 3×3 convolutional layers into 3×1 and 1×3 convolutional layers (45), the $C \times T$ of the original convolutional layer is decomposed into $C \times 1$ and $1 \times T$. This decomposition scheme can not only reduce the number of parameters, increase the width and depth of the network, and capture long-range dependencies, but also increase the nonlinear feature extraction capability, thereby improving the efficiency and performance of the model.

By using two convolutions to extract spatial and temporal features, two different connection strategies were emerged. In the first way, the temporal features are extracted first, and then the spatial features are extracted, as shown in Figure 2D; In the second way, the spatial features are extracted first, followed by the temporal features, as shown in Figure 2E. Among them, in the first connection method, the temporal convolution section uses 10 filters with filter sizes of 64, 40, 26, 16, and the spatial convolution part uses 20 filters with filter sizes of 8, 6, 4, 2, respectively. In the second connection method, 10 filters are used in the spatial convolution section and 20 filters are used in

the temporal convolution section, and the filter size is consistent with the above.

In addition, the model also contains a layer of spatial feature convolution after the spatiotemporal feature convolution. This layer extracts spatial features while reducing the dimension of the feature map. Through such a design, we anticipated the model to comprehensively capture the spatiotemporal features in EEG signals, efficiently decrease computational complexity, and enhance the model's overall performance and efficiency.

2.3.1.3 Attention mechanism

Attention mechanism is a technology that emulates human attention processes, which has grown in significance within the domains of natural language processing and deep learning in recent years (46). The technology enables machines to handle large-scale data and complex tasks more intelligently by simulating human focus and the ability to selectively process information. At present, the attention mechanism has become a widely used tool for deep learning (47, 48). Integrating the attention mechanism module into the convolutional network can help it automatically select and focus on important features in the data, and improve the model's ability to extract and represent key information. In this study, we employed three commonly used attention mechanisms: Squeeze-and-Excitation Networks (SE) (49), Convolutional Block Attention Module (CBAM) (50), and Efficient Channel Attention (ECA) (51). Among them, the relevant parameters of SE are set to: reduction = 1; the relevant parameters of CBAM are set to: reduction = 1, kernel_size = 7; and the relevant parameters of ECA are set to: kernel_size = 3. The principles of each of the three attention mechanisms are detailed below.

2.3.1.3.1 SE

SE (Squeeze-and-Excitation Networks) is a convolutional neural network model designed to enhance the model's ability to pay attention to crucial features from the input data. The core idea of SE is to add an attention module channel on top of the CNN. The module consists of two pivotal parts: a squeeze segment and an excitation segment, and its framework is shown in Figure 3.

Squeeze: SE uses global average pooling to compress each channel's feature map into a scalar, which reduces the dimension of the feature map and captures global statistics between channels. If the input is a feature map $X \in \mathbb{R}^{C \times H \times W}$, the compressed feature map is $Z \in \mathbb{R}^{C \times 1 \times 1}$, Z_C is the c -th element of Z can be calculated as Equation (1):

$$Z_C = F_{sq}(X_C) = \frac{1}{H \times W} \sum_{i=1}^H \sum_{j=1}^W X_C(i, j) \quad (1)$$

F_{sq} represents the squeeze operation, where H and W denote the feature map's height and width. In our EEG data, the channel and time correspond, respectively. $X_C(i, j)$ stands for the value on the feature map with a height dimension of i and a width dimension of j .

Excitation: to take advantage of the information gathered by squeeze, use excitation operations to capture channel dependencies. The excitation operation mainly obtains the attention weight S by nonlinear mapping by input of the compressed feature Z to the fully connected layer can be calculated as Equation (2):

$$S = F_{ex}(Z) = \sigma(W_2 \delta(W_1 Z)) \quad (2)$$

F_{ex} represents the excitation operation, δ represent to the ReLU function, $W_1 \in \mathbb{R}^{C/r \times C}$ and $W_2 \in \mathbb{R}^{C \times C/r}$, r is the reduction ratio. W_1 and W_2 are the weight parameters of the descending and ascending fully connected layer, and the σ represents the Sigmoid function, which limits the input value to the range of 0 and 1. The final output $\tilde{X}_C$ is derived from the feature map X_C rescaling transformation as Equation (3):

$$\tilde{X}_C = F_{scale}(X_C, S_C) = S_C \cdot X_C \quad (3)$$

2.3.1.3.2 CBAM

Convolutional Block Attention Module (CBAM) contains two submodules: the channel attention module (CAM) and the spatial attention module (SAM), as is depicted in Figure 4. CAM and SAM are used to strengthen the model's attention capability to different channels and different spatial locations of the input feature map, respectively.

CAM: This module first obtains the average and maximum values of each channel by averaging pooling and maximizing pooling operations on the input feature map. These values are then processed by a hidden layer of Multilayer Perceptron (MLP) to learn and generate weights for each channel. Finally, the sum and merge of each element to obtain the channel attention degree $M_C(F)$. For the input feature map $F \in \mathbb{R}^{C \times H \times W}$, after passing through the CAM $M_C(F) \in \mathbb{R}^{C \times 1 \times 1}$ can be calculated as Equation (4):

$$M_C(F) = \sigma(MLP(AvgPool(F)) + MLP(MaxPool(F))) \quad (4)$$

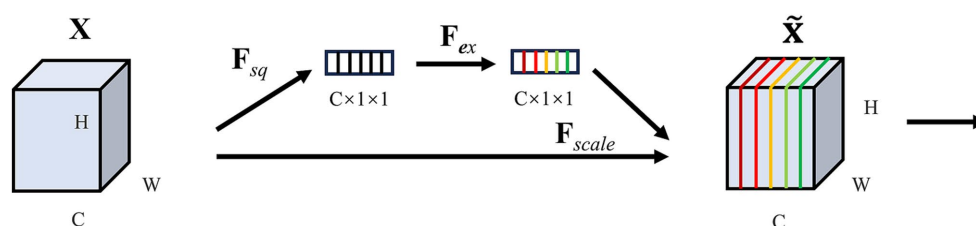


FIGURE 3

Structure of SE. F_{scale} represents channel-wise multiplication.

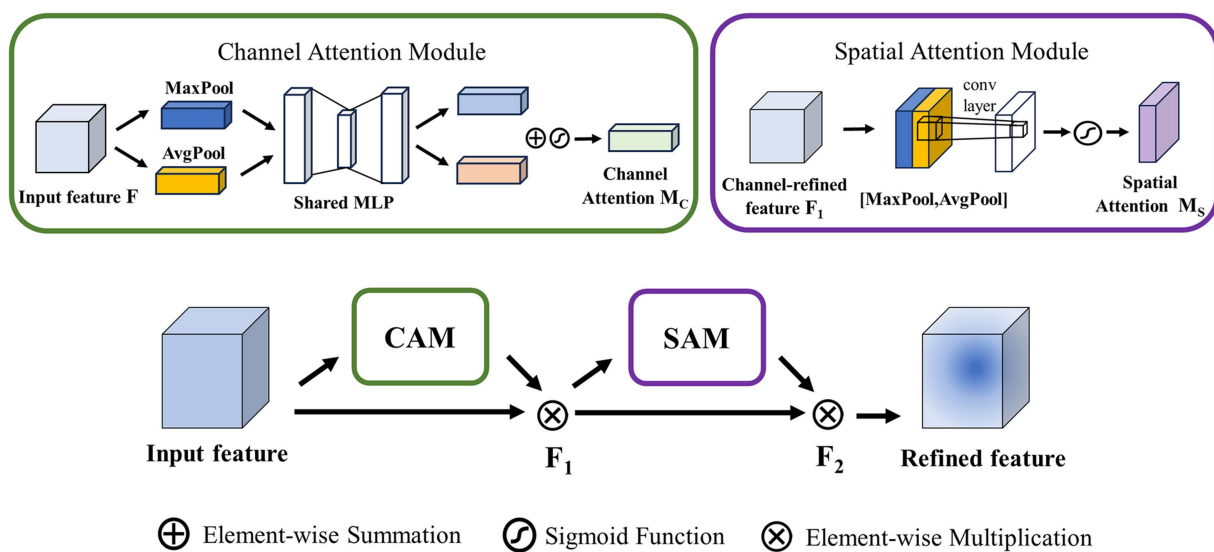


FIGURE 4
Structure of CBAM.

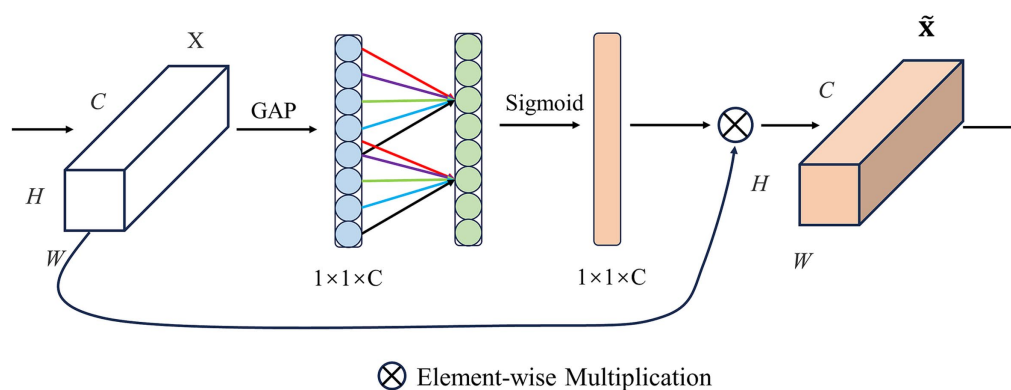


FIGURE 5
Structure of ECA.

AvgPool signifies the average pooling operation, MaxPool signifies the maximum pooling operation, MLP stands for multilayer perceptron, and σ refers to the Sigmoid function.

SAM: This module is mainly concerned with the location of the information, which complements the CAM. To calculate spatial attention, the SAM uses average pooling and maximum pooling across the channel axis with convolution to generate spatial feature maps. Unlike channel attention, spatial attention does not use MLP, but instead employs convolution to process spatial feature maps. For input feature map $F_1 \in \mathbb{R}^{C \times H \times W}$, after passing through the SAM $M_S(F_1) \in \mathbb{R}^{1 \times H \times W}$ can be calculated as Equation (5):

$$M_S(F_1) = \sigma \left(f^{7 \times 7} \left([\text{AvgPool}(F_1); \text{MaxPool}(F_1)] \right) \right) \quad (5)$$

Where f stands for the convolution operation, 7×7 is the convolution kernel size, and σ refers to the Sigmoid function.

The final output feature map is calculated by CAM and SAM. The output map $M_C(F)$ after CAM is multiplied element by element with the input feature map F to generate feature F_1 , and F_1 is multiplied element by element with the output diagram $M_S(F_1)$ after SAM to generate the final output feature map F_2 .

2.3.1.3.3 ECA

Efficient Channel Attention (ECA) is commonly used in image classification tasks based on SE, as shown in Figure 5. The core idea of ECA is to use one-dimensional convolution operations to model relationships between channels instead of traditional fully connected layer operations, which can significantly reduce calculations, model parameters, and improve the calculation efficiency of the model. Similar to SE, ECA uses global average pooling (GAP) to aggregate spatial information for channels. Then, by performing a one-dimensional convolution operation on the feature map after global average pooling, all channels share learning parameters and quickly extract the relationship between channels, thereby enhancing

the performance of channel attention which can be calculated as Equation (6):

$$\omega = \sigma(C1D_k(GAP(X))) \quad (6)$$

C1D stands for one-dimensional convolution operation, k is the one-dimensional convolution kernel size, and σ is the Sigmoid function. The use of one-dimensional convolution not only reduces model complexity, but also ensures efficiency and effectiveness through local cross-channel interaction. Finally, ω is multiplied by X element by element results in the final feature map $\tilde{X}$.

2.3.2 Feature classification layer

The input of the feature classification layer is the feature map obtained after passing through the spatial feature convolutional layer. There are four steps in this layer. Firstly, the input feature map undergoes the application of the nonlinear function Square, and then downsampling is performed through the average pooling layer to reduce the dimensionality of the feature map while retaining the main feature information. Secondly, the nonlinear function Log for activation is used to extract features related to EEG bands after the averaging pooling layer. Thirdly, the dropout layer is introduced to prevent the model from overfitting. The dropout layer can randomly omit the output of some neurons during training, thereby reducing the dependence between neurons. Ultimately, the fully connected layer is utilized to finalize the classification.

2.4 Network training

For the MSTCNN model, the batch size was set as 32 and the 200 epochs were trained for early stopping. Early stopping strategy was triggered when the value of the loss function no longer decreases in 10 consecutive epochs. CrossEntropy was chosen as the loss function, and AdamW optimizer was used for gradient optimization. In terms of the MSTCNN's learning rate, the warm-up strategy was adopted shown in Figure 6, which starts

with the learning rate set to $8e-5$, gradually increases to $1e-3$ after 10 warm-up rounds, and finally gradually decreases to $3e-5$. By employing the learning rate warm-up strategy, the training speed can be accelerated, and the convergence and performance of the network can be improved. Applying a larger learning rate in the initial epochs can help the model find the global optimal solution or regions closer to the optimal solution in the parameter space more quickly. As the train continues execution, the learning rate gradually decreases, which is conducive to the training of stable networks.

2.5 Evaluation methods

Use cross-validation to evaluate the model's performance and generalization ability. Nine folds of data were used for training and one fold of data for testing. Accuracy, Precision, Recall, and F₁Score were computed to evaluate model performance as Equations (7–10). Specifically, True Positives (TP) indicates positive samples correctly classified, False Positives (FP) indicates negative samples incorrectly classified as positive, True Negatives (TN) indicates negative samples correctly classified, and False Negatives (FN) indicates positive samples incorrectly classified as negative.

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \quad (7)$$

$$Precision = \frac{TP}{TP + FP} \quad (8)$$

$$Recall = \frac{TP}{TP + FN} \quad (9)$$

$$F_1 \text{ Score} = \frac{2TP}{2TP + FP + FN} \quad (10)$$

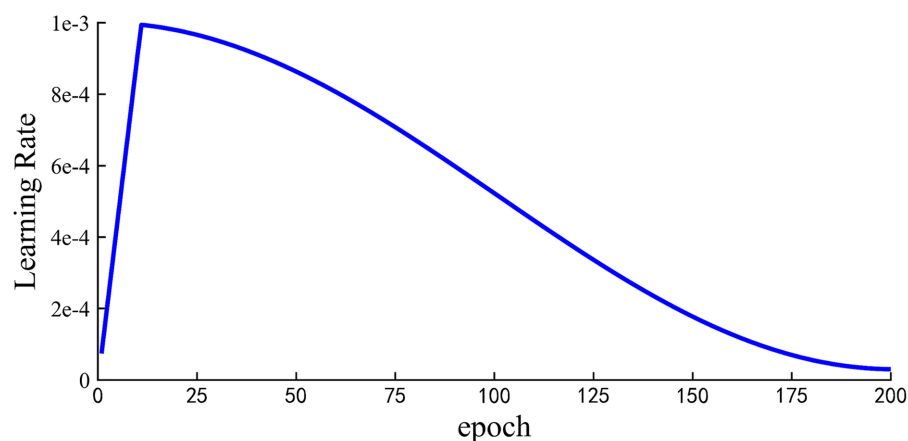


FIGURE 6

Learning rate setting during model training with warming strategy. Total trained in 200 epochs.

3 Results

The results of different multi-scale convolutional structures for GAD detection are given in Table 1. The model with only temporal convolution obtained an accuracy of 96.75%, a precision of 96.69%, a recall of 97.68% and a F₁Score of 97.18%. In order to enhance the generalization ability and nonlinear expression ability of the multi-scale CNN model in convolutional feature extraction, Convolution + batch normalization + ReLU structure was added in the model. The accuracy improved to 98.25%. Therefore, all other comparison models adopted the Convolution + batch normalization + ReLU structure. Further, we introduced spatial convolution and explored different combinations of temporal and spatial convolution for comparisons. The results showed that the combination with spatial + temporal convolutions (named MSTCNN) yielded superior performance, achieving an accuracy of 99.19%, a precision of 99.45%, a recall of 99.14% and a F₁Score of 99.29%.

Several classic models also used to verify the effectiveness of our model. The compared models of EEGNet, multi-resolution CNN (MRCNN), and CNN-LSTM, yielded average accuracies of $94.34 \pm 0.75\%$, $96.35 \pm 0.42\%$, and $97.26 \pm 0.86\%$ on our datasets, respectively. The specific classification evaluation indicators of each model are shown in Table 2.

Based on our proposed convolutional structure (SpaConv + TemConv + BR), three commonly used attention mechanisms (SE, CBAM, and ECA) were added into the model. As shown in Table 3,

our MSTCNN model shows performance improvement following the inclusion of attention mechanisms and yielded more stable results. In particular, the improvement effect of the SE attention mechanism was the most significant, with the highest accuracy of 99.48%.

Besides, the impacts of five different frequency bands (Theta, Alpha1, Alpha2, Beta1, and Beta2) were explored on the classification of GAD and HC with MSTCNN-SE model. As indicated in Table 4, the accuracy of the Theta band and the Alpha1 band is lower with a classification accuracy of less than 90%. With the increase of frequency band, the classification accuracy also gradually improved, and the highest classification accuracy of 97.45% was achieved on the Beta2 band.

Based on the results of Table 4, that is, high accuracy can be obtained with the high-frequency EEG rhythm. Three high-frequency EEG bands, including 13-30 Hz, 10-30 Hz, and 8-30 Hz, were extracted for GAD diagnosis. The results are presented in Table 5. It shows that 10-30 Hz can gain consistent accuracy compared with 4-30 Hz, which has no statistically significant difference (see Table 6).

4 Discussion

This study proposed a novel end-to-end multi-scale Spatial–Temporal local sequential and global parallel convolutional neural network called MSTCNN and applied it to diagnose GAD by

TABLE 2 Classification performances of different convolution methods.

Models	Accuracy (%)	Precision (%)	Recall (%)	F ₁ Score (%)
TemConv	96.75 ± 0.68	96.69 ± 1.20	97.68 ± 0.65	97.18 ± 0.56
TemConv + BR	98.25 ± 0.35	98.19 ± 0.51	98.76 ± 0.47	98.47 ± 0.31
TemSpaConv + BR	97.43 ± 0.85	98.19 ± 0.99	97.33 ± 1.56	97.75 ± 0.73
TemConv + SpaConv + BR	98.64 ± 0.32	98.75 ± 0.71	98.88 ± 0.52	98.81 ± 0.26
SpaConv + TemConv + BR (MSTCNN)	99.19 ± 0.40	99.45 ± 0.47	99.14 ± 0.49	99.29 ± 0.34

“TemConv” means temporal convolution. “BR” means adding BatchNorm and ReLU functions after the convolution. “TemSpaConv” means that the temporal convolution and the spatial convolution are in the same convolutional kernel. “TemConv + SpaConv” means the temporal convolution followed by the spatial convolution. “SpaConv + TemConv” means the spatial convolution followed by the temporal convolution. The bold values provided in the table represent the best results compared with others.

TABLE 3 Classification performances of classical deep learning models.

Models	Accuracy (%)	Precision (%)	Recall (%)	F ₁ Score (%)
EEGNet (52)	94.34 ± 0.75	95.80 ± 1.23	94.26 ± 2.02	95.00 ± 0.71
MRCNN (53)	96.35 ± 0.42	96.28 ± 1.22	97.40 ± 1.46	96.82 ± 0.44
CNN-LSTM (54)	97.26 ± 0.86	98.32 ± 1.01	96.89 ± 2.14	97.57 ± 0.81
Our model	99.19 ± 0.40	99.45 ± 0.47	99.14 ± 0.49	99.29 ± 0.34

The bold values provided in the table represent the best results compared with others.

TABLE 4 Classification performances of different attention mechanisms.

Models	Accuracy (%)	Precision (%)	Recall (%)	F ₁ Score (%)
MSTCNN-SE	99.48 ± 0.23	99.66 ± 0.23	99.43 ± 0.28	99.55 ± 0.20
MSTCNN-CBAM	99.34 ± 0.38	99.31 ± 0.54	99.54 ± 0.33	99.42 ± 0.33
MSTCNN-ECA	99.46 ± 0.20	99.61 ± 0.22	99.44 ± 0.46	99.52 ± 0.18

MSTCNN-SE/CBAM/ECA means adding SE Attention, CBAM Attention, or ECA Attention for MSTCNN model. The bold values provided in the table represent the best results compared with others.

TABLE 5 Classification performances of different frequency bands with MSTCNN-SE model.

Frequency band	Accuracy (%)	Precision (%)	Recall (%)	F ₁ Score (%)
Theta	88.09 ± 1.09	89.08 ± 2.30	90.34 ± 2.16	89.66 ± 0.99
Alpha1	86.35 ± 1.12	88.53 ± 1.93	87.52 ± 2.17	87.99 ± 1.10
Alpha2	93.56 ± 0.76	93.45 ± 1.05	95.46 ± 1.54	94.43 ± 0.67
Beta1	96.26 ± 0.48	96.69 ± 1.08	96.79 ± 0.72	96.73 ± 0.41
Beta2	97.45 ± 0.43	98.08 ± 0.86	97.46 ± 1.19	97.76 ± 0.41

TABLE 6 Classification performances of extended frequency bands with MSTCNN-SE model.

Frequency band	Accuracy (%)	Precision (%)	Recall (%)	F ₁ Score (%)
13–30 Hz	98.90 ± 0.29	99.13 ± 0.34	98.95 ± 0.56	99.04 ± 0.25
10–30 Hz	99.47 ± 0.24	99.48 ± 0.37	99.59 ± 0.28	99.54 ± 0.20
8–30 Hz	99.42 ± 0.26	99.48 ± 0.47	99.52 ± 0.29	99.50 ± 0.22

The bold values provided in the table represent the best results compared with others.

utilizing multichannel EEG signals. The main findings are as follows. Firstly, the proposed MSTCNN combined with SE attention mechanism obtained an excellent classification performance on the collected EEG data, with an accuracy of 99.48%, a precision of 99.66%, a recall rate of 99.43%, and a F1 Score of 99.55%. Secondly, an interesting phenomenon was stumbled upon: the high-frequency band holds significant importance in diagnosing GAD, and higher frequency band can obtain higher accuracy in GAD recognition. Notably, the accuracy of the 10–30 Hz band is consistent with the 4–30 Hz band. Detailed discussion will be presented next.

4.1 Best classification performance from MSTCNN model

When applying deep learning to extract features from EEG signals, researchers mostly focus on multi-scale convolution in the temporal domain and ignore the spatial relationships between channels (42–44). Introducing multi-scale spatial convolution can extract spatial features more efficiently, thereby improving model performance. In this study, we explored the method of multi-scale spatial-temporal convolution and found that the spatial axis decomposition idea of splitting a single convolution kernel into two convolutions can achieve better results. This idea can not only effectively reduce the complexity of the model and decrease the risk of overfitting, but also improve the computational efficiency (45). Furthermore, we compared the effects of convolutional sequences with different spatial and temporal convolutions. It has been presented in Table 1 that the accuracy of spatial convolution combined with temporal convolution is 0.55% higher than that of temporal convolution combined with spatial convolution. Since there is spatial convolution after the spatial-temporal convolution module, it can effectively avoid redundant operations in the spatial dimension.

We also tried to validate the effectiveness and accuracy of our proposed MSTCNN Model for GAD detection. On the one hand, some classical deep learning models was used to compare with

our models. Among them, EEGNet is a concise deep learning model commonly used to process EEG data, which can efficiently extract features and use them for classification (52). In our study, EEGNet model obtained an accuracy of 94.34%. Next, we tried the MRCNN model proposed by Eldel et al. for sleep EEG data (53), and its accuracy in our classification task reached 96.35%. Finally, CNN-LSTM model proposed by Wang et al. (54) was used to classify our data, and obtained an accuracy of 97.26%. The above results indicate that the multi-scale spatial-temporal convolution strategy proposed in this study outperforms conventional deep learning models, leading to exceptional achievements. On the other hand, our results were compared with other similar studies. Park et al. used machine learning in major psychiatric disorders based on resting EEG and obtained an accuracy of 91.03% (55). Al-Ezzi et al. used a deep learning model (CNN-LSTM) for three different degrees of anxiety and HC based on task-state EEG data, and obtained the accuracy of 92.86%, 92.86%, 96.43%, and 89.29%, respectively (37). Mohan et al. used CNN to discriminate depressed and anxiety patients based on EEG and obtained an accuracy of 97.6% (56). It is worth mentioning that our previous study, combining features extraction and machine learning model, obtained an accuracy of 97.83% for GAD and HC (20). MSTCNN model, to the best of our knowledge, has achieved the highest accuracy for GAD and HC detection compared with advanced models and existed studies. In summary, MSTCNN has outstanding advantages in classification performance. These findings not only verify the effectiveness of our proposed model, but also provide support for its potential advantages in subsequent clinical application for GAD diagnosis.

4.2 MSTCNN improved with attention mechanisms

EEG signals contain a wealth of information, which poses challenges to signal processing, feature extraction, and classification. To efficiently extract features and obtain excellent classification performance, the attention mechanisms were

employed in combination with MSTCNN. Specifically, we incorporated and evaluated three widely used attention mechanisms (SE, CBAM, and ECA) into the convolution. At present, the attention mechanism has gradually become a boom in deep learning, and an increasing number of researchers are applying it to EEG signal processing. Deng et al. (57) improved the accuracy of major depressive disorder classification from 91.24% to 94.37% by adding SE attention mechanism to one-dimensional convolution. Chen et al. used CBAM attention for ResNet34 in emotion recognition task, and the accuracy increased by 5.54% compared with ResNet34 (58). Jia et al. (59) proposed a spectral-temporal convolutional neural network with ECA attention, and the classification results showed that there was also a significant increase for the classification performance. By introducing these attention mechanisms, MSTCNN model can focus on more important features, further optimize the feature extraction process and enhance the performance and stability of the model.

4.3 Deep learning reveal the key frequency band for GAD diagnosis

Previous studies have reported a clear correlation between EEG rhythms and alternate EEG features in GAD patients (60). Additionally, our previous research has pointed to the importance of beta rhythms in GAD (20). Significantly higher accuracy was obtained for Beta rhythms in the high-frequency band compared to Theta and Alpha in the low-frequency band. Beta rhythms are associated with functions such as attention, cognitive control, and emotion regulation in the brain (61). Given that GAD often accompanies mood fluctuations, which may be the reason why beta sub-bands are prone to exhibit high accuracy in GAD and HC classification. In summary, different frequency bands had a significant impact on the classification results of GAD. A more universal regularity is that the higher the frequency range, the better the GAD classification performance.

Based on the above findings, we attempted to expand the frequency bands to further explore key frequency bands for distinguishing GAD. Three extended frequency bands were extracted in this study: 13–30 Hz, 10–30 Hz, and 8–30 Hz. In contrast to the results of Beta2, the classification accuracy is considerably improved when using the 10–30 Hz frequency band with the accuracy of 99.47%, which has no statistical difference with the accuracy of the 4–30 Hz frequency band ($F=0.0099$, $p=0.92$; which was tested by one-way analysis of variance. If p is less than 0.05, there is a significant difference between groups. Otherwise, there is no significant difference). Wen et al. used the CNN model and EEG signals to identify cognitive impairment diseases, and also achieved the highest classification accuracy through three frequency band combinations (10–30 Hz) compared with other combinations (62). To the best of our knowledge, no prior research has utilized deep learning methods to explore the impact of different combined frequency bands on GAD classification. Our current results provide preliminary evidence supporting the importance of high-frequency bands in GAD identification and highlight the prominent advantages of

the 10–30 Hz band. These findings will contribute to a more comprehensive understanding of the relationship between EEG frequency bands and GAD, and provide a new insight for the GAD diagnosis. The excellent classification performances of GAD detection at high frequencies can provide guidance for subsequent practical applications. For instance, we may choose to filter out low frequencies to effectively mitigate the noise and interference stemming from those bands when developing an EEG-based system for GAD diagnosis.

4.4 Limitation

Although the MSTCNN proposed in this study has demonstrated impressive capabilities in the identification of GAD and HC, it still has come with certain limitations. Firstly, the main manifestation is the sample size utilized in the study is relatively limited (45 participants for GAD and 36 participants for HC), which limits our effective verification of the robustness and generalization ability of the model. Secondly, our deep learning model appears to lack reasonable interpretability for GAD diagnosis. Thirdly, in real-life scenarios, the process in which hospitals collect EEG data may be some discrepancies, such as different EEG acquisition equipment and inaccurate placement of electrodes, which may lead to diagnostic performance decline. To more comprehensively evaluate the performance and generalization ability of the model, we will try to use more diverse data sources and explore deep learning model interpretability in follow-up studies.

5 Conclusion

In this study, an end-to-end deep learning MSTCNN model was proposed for the precise diagnosis of GAD based on EEG signals. Three widely used attention mechanisms were applied on MSTCNN model for the improvements of the classification performances. And different frequency bands were extracted to explore key frequency band in GAD diagnosis. Notably, MSTCNN combined with the attention mechanism of Squeeze-and-Excitation Networks achieved an excellent classification performance, to the best of our knowledge, with the highest accuracy of 99.48%. More interestingly, it is found that higher frequency band can obtain higher accuracy in GAD recognition. The accuracy of the high-frequency band with 10–30 Hz has no statistical difference with the accuracy of the 4–30 Hz frequency band. This finding could simplify the signal processing process and reduce the complexity of low-frequency EEG data processing. In sum, this work can have a positive impact on the precise diagnosis of GAD and move a step forward towards the automatic diagnostic system of GAD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Zhejiang Normal University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WL: Writing – original draft. GL: Writing – review & editing. ZH: Writing – original draft. WJ: Writing – review & editing. XL: Writing – review & editing. XX: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A neuroimaging study of brain activity alterations in treatment-resistant depression after a dual target accelerated transcranial magnetic stimulation

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In this study, we designed a new transcranial magnetic stimulation (TMS) protocol using a dual-target accelerated transcranial magnetic stimulation (aTMS) for patients with treatment resistant depression (TRD). There are 58 TRD patients were recruited from the Second People's Hospital of Guizhou Province, who were, respectively, received dual-target (real continuous theta burst stimulation (cTBS) at right orbitofrontal cortex (OFC) and real repetitive transcranial magnetic stimulation (rTMS) at left dorsolateral prefrontal cortex (DLPFC)), single-target (sham cTBS at right OFC and real rTMS at left DLPFC), and sham stimulation (sham cTBS at right OFC and sham rTMS at left DLPFC). Resting-state functional magnetic resonance imaging (rs-fMRI) was acquired before and after aTMS treatment to compare characteristics of brain activities by use of amplitude of low-frequency fluctuations (ALFF), fractional low-frequency fluctuations (fALFF) and functional connectivity (FC). At the same time, Hamilton Depression Scale-24 (HAMD₂₄) were conducted to assess the effect. HAMD₂₄ scores reduced significantly in dual group comparing to the single and sham group. Dual-target stimulation decreased not only the ALFF values of right fusiform gyrus (FG) and fALFF values of the left superior temporal gyrus (STG), but also the FC between the right FG and the bilateral middle frontal gyrus (MFG), left triangular part of inferior frontal gyrus (IFG). Higher fALFF value in left STG at baseline may predict better reaction for bilateral aTMS. Dual-target stimulation can significantly change resting-state brain activities and help to improve depressive symptoms.

KEYWORDS

treatment-resistant depression, transcranial magnetic stimulation, resting-state functional magnetic resonance imaging, amplitude of low-frequency fluctuations, fractional amplitude of low-frequency fluctuations, functional connectivity

1 Introduction

Depression, manifested as marked and persistent low mood that is not commensurate with the environment, is a serious global public health problem. In recent years, with the increasing pressures of modern life and continuous improvement in disease diagnosis skill, it is found that the population of patients suffering from depression is consistently expanding worldwide. According to a World Health Organization (WHO) report (1), there are approximately 350 million patients with depression of different ages currently. This highly prevalent disorder also has high rates of disability, recurrence, mortality, and heritability (2, 3). As a result, individuals, family, and society need to face the huge economic and emotional burden imposed by the recurrence and sequelae of depression. Given the damage to the public, improving treatments and extending the long-term prognosis of depressive patients are urgently needed.

At present, the main treatment methods for depression include medication, psychotherapy and physical therapy. However, approximately one-third to two-thirds of patients still do not respond to medication, which is known as treatment-resistant depression (TRD) patients (4–7). TRD is typically defined as low efficacy of two or more antidepressants with different chemical structures at adequate dosages and courses (8–10). Therefore, in recent years, researchers have begun to explore another method, especially physical one, to improve capacity for treating TRD. Some of these studies reported that nonpharmacological treatments have a durable effect than medication (11–13). Among the nonpharmacological therapies, transcranial magnetic stimulation (TMS) is a safe, non-invasive, and painless way that was approved by the U.S. Food and Drug Administration (FDA) in 2008 for the treatment of depression (14). However, traditional repetitive transcranial magnetic stimulation (rTMS) treatment usually takes several weeks and shows limited efficacy. To further improve the treatment efficiency and exclude the influence of other factors, such as drugs and psychotherapy, some researchers have begun to pay their attention to accelerated repetitive transcranial magnetic stimulation (arTMS). Because it could compress the treatment cycle from weeks into a few days while maintaining safety and effectiveness, arTMS not only greatly reduces the suffering of patients but also decreases the time required for treatment and improves efficiency (15).

The brain of human is a complicated structure, because different brain regions perform their own functions and coordinate to complete complex functions, such as perception, processing, and action execution etc. Quite a few numbers of studies have been committing to detect some brain areas as the stimulation targets which are related to the effect of TMS and to improve the efficacy of TMS for treating TRD by using different stimulation parameters. At present, the FDA has approved the TMS targeted at the left dorsolateral prefrontal cortex (DLPFC), which is a key area in depressive symptoms and shown to be hypoactive in major depressive disorder, for the treatment of depression (16–18). The efficacy of this traditional protocol is limited even though it takes several weeks. Considering that the effect of current treatment protocols is still limited, it is needed to explore more possible programs. Some new studies showed that bilateral rTMS treatment was more effective for treating depressive symptoms than unilateral, sham stimulation or medicine only (19, 20). We noticed that the

lateral orbitofrontal cortex (IOFC), related to non-reward system, is implicated in the rumination of sad events and memories in depression patients this indicated that the IOFC is a crucial target for the improvement of depression (21–25). Thus, this study researched the effect of a new stimulation protocol targeted at the left DLPFC and right IOFC and the changed of functional magnetic resonance imaging (fMRI) before and after the treatment.

Resting-state functional magnetic resonance imaging (rs-fMRI) has been used to explore the spontaneous activity in brains and neurobiological mechanisms in depressed patients by diverse analysis methods which have been mainly divided into the functional segregation and integration (26–28). The former includes amplitude of low-frequency fluctuations (ALFF), fractional amplitude of low-frequency fluctuations (fALFF), etc. In 2007, Zang et al. suggested that the ALFF, which assessed oscillation by measuring the blood-oxygen-level dependent (BOLD) signals in the low-frequency range (0.01 ~ 0.08 Hz) based on the voxel level, reflected spontaneous neural activity in specific brain areas (29). Compared with other methods of analysis, fractional amplitude of low-frequency fluctuations (fALFF) is a more useful way for measuring the spontaneous activity of the resting brain with fewer physiological noise and nonspecific signals (30). The later embraces graph theory, seed-based analysis, independent component analysis (ICA) and so on (26). Graph theory describe the relationship between nodes and edges depend on node degree, centrality, average path length, etc. (31–34), where nodes can be the electrodes and channels of electroencephalogram and magnetoencephalography or the common region of interest (ROI) defined on structural and functional template, while the edge refers to connections between the nodes (35). Seed-based analysis mainly focuses on the correlation between one ROI to another one refers to the synchronous activity between different brain regions and indicates whether these two brain regions are related in terms of function (26, 29). ICA helps to extract different networks and analysis simultaneous voxel to voxel interactions among networks (26, 28). In this study, our team will analyze the differences in brain activity of depressive patients before and after receiving different arTMS from the both perspectives of separation and integration.

We conducted arTMS treatment for the TRD patients aimed at left DLPFC and right IOFC, a brain area related to the reward mechanisms, and collected brain functional images of subjects before and after treatment using rs-fMRI. Then, the neural activity was evaluated by ALFF, fALFF, and FC value before and after arTMS.

2 Methods

2.1 Participants and groups

This study was approved by the Ethics Committee of the Second People's Hospital of Guizhou Province. From August 2021 to July 2022, 60 patients with TRD were recruited from this hospital. Subjects or their legal guardians agreed to participate in this study and signed the informed consent form. This trial was prospectively registered in the China Clinical Trial Registry (Registration number: ChiCTR2100049002).

The inclusion criteria were as follows: (1) met criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) diagnostic for MDD; (2) were right-handed; (3) were 18 to

60 years old (regardless of sex); (4) had an HAMD24 score ≥ 21 ; (5) previously received a full course of two or more antidepressant drugs at a sufficient dosage but achieved little or no treatment response; and (6) signed informed consent form.

The exclusion criteria were as follows: (1) with psychotic symptoms or any other mental disorders; (2) with symptoms caused by organic diseases or medications; (3) with severe organic disease; or (4) with contraindications for TMS or MRI, such as a history of epilepsy, pregnancy within 3 months, an artificial heart valve or a pacemaker.

2.2 Intervention

In this study, we adopted the following arTMS treatment protocol to reduce the traditional 4–5 weeks period of stimulation to 5 days by delivering multiple stimulations per day. The specific procedure was as follows: first, cTBS at 5 Hz was applied to the right OFC for a total of 48 s, which included 600 pulses and a resting motor threshold (RMT) of $100\% \pm 10\%$. Then, high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) at 20 Hz was applied to the left DLPFC for 90 s, which included 1,800 pulses and an RMT of $100\% \pm 10\%$. The above stimulations were performed 4 times a day, with 50-min intervals between each series, for 5 consecutive days. Thus, the right OFC target received a total of 12,000 pulses, and the left DLPFC target received a total of 36,000 pulses during the full course.

Patients in these three groups received different arTMS stimulations with the same parameters described above. In the dual group, real stimulation was applied to both the right OFC and left DLPFC. However, in the single group, the subjects received sham stimulation treatment with a fake figure-eight coil that mimicked the real one at right OFC and received real stimulation at the left DLPFC. In the sham group, the subjects received sham stimulation treatment with a fake figure-eight coil at both the right OFC and left DLPFC.

2.3 Assessment indicators

All subjects completed the Hamilton Depression Scale-24 (HAMD24), which is widely used in clinical diagnosis because of its good reliability and validity, before and after arTMS intervention, 1 week after intervention, and 4 weeks after intervention to assess the depressive symptoms. Before and after arTMS, resting-state fMRI was used to observe spontaneous brain activity in fALFF and Δ fALFF in different brain regions. Then, regions with significant differences after arTMS were selected as regions of interest (ROIs), and with this as the center, ROI of $r=6$ mm was used as the seed point, and the voxel-wise functional connectivity of TRD depression patients was calculated.

2.4 Image acquisition

The acquisition of rs-fMRI image data in this study was completed by professional technicians with intermediate or higher professional titles in the imaging department in an examination room. The data were collected by a high-field magnetic resonance scanner from GE

(manufacturer's model: SIGNA HDe) (Coil: General Electric, Madison, WI, USA).

During the scan, all patients were asked to remain calm and awake; keep their eyes closed; and refrain from moving their head. The collection of rs-fMRI data in this study utilized the following two specific scanning sequences: (1) 3D-T1-weighted whole-brain structure imaging with a fast spoiled gradient echo (FSPGR) sequence (slices = 116, slice thickness = 1.2 mm, repetition time (TR) = 12.536 ms, echo time (TE) = 5.432 ms, inversion time = 350, flip angle (FA) = 20° , and matrix = 256×256). (2) resting-state fMRI using a gradient echo and echo planar imaging (GRE-EPI) sequence (slices = 28, slice thickness = 3.5 mm, TR = 2,500 ms, TE = 40 ms, time points = 300, FA = 90° , and matrix = 80×80).

2.5 Rs-fMRI data processing

Related data were analyzed by Data Processing and Analysis for Brain Imaging (DPABI) software (36), which was based on the MATLAB_2013b environment. The following 12 steps were used: (1) conversion from DICOM to NIFTI, (2) removal of the first ten time points to reduce inaccuracy resulting from head movement or other factors at the beginning of scans, (3) slice timing correction to preventing interference between adjacent slices by adopting interval scanning, (4) realignment (checking and correcting the head motion), (5) nuisance regression (removing another covariate), (6) transformation to Montreal Neurological Institute (MNI) space, (7) detrending (removing the noise of the machine), (8) smoothing (reducing the effects of spatial noise and reducing differences in brain structure between subjects), (9) calculation of ALFF (0.01–0.08 Hz) and fALFF values to reflect the spontaneous resting-state activity of each different brain region (ALFF and fALFF maps were standardized by z score-transformation into zALFF and zfALFF maps), (10) quality control (evaluating the quality of images and excluding the subjects whose images did not meet the quality requirements), and (11) calculation of FC (brain regions with the cluster voxels size >40 in the corrected ALFF and fALFF results were selected as ROIs for further analysis of the FC between the ROIs and whole brain).

2.6 Statistical analysis

SPSS 29.0 software was used to perform the chi-square test to assess the influence of sex on the three groups, and one-way analysis of variance (ANOVA) was performed to explore the influence of age, education level and HAMD24 scores of the three groups. A p value less than or equal to 0.05 was considered statistically significant. We extracted the time courses of brain regions with abnormal ALFF and fALFF values and then conducted correlation analysis in SPSS software to calculate the Pearson correlation coefficient between the difference in HAMD24 scores (Δ HAMD24) with ALFF or fALFF.

The DPABI software (36) was used to perform statistical analysis of images with the following steps: (1) paired t test: To calculate ALFF and fALFF values and to identify ROIs that significantly differed at pre-TMS and post-TMS in the three groups, we applied the paired t test in DPABI software (36). (2) Multiple comparisons: gaussian random field (GRF) correction with a voxel p value of 0.002 and cluster p value of 0.1 was used to determine two-tailed significant

TABLE 1 Comparison of HAMD24 scores among dual, single and sham groups.

Variables	dual (<i>n</i> = 19) Mean $\pm$ SD	single (<i>n</i> = 19) Mean $\pm$ SD	sham (<i>n</i> = 20) Mean $\pm$ SD	<i>p</i> value
Age (years)	27.58 $\pm$ 9.605	26.32 $\pm$ 8.845	28.70 $\pm$ 10.887	0.752 ^a
Gender (male/female)	4/15	3/16	5/15	0.776 ^b
Education (years)	4.80 $\pm$ 6.815	4.66 $\pm$ 5.800	2.38 $\pm$ 1.804	0.272 ^a
HAMD ₂₄ (pre)	49.16 $\pm$ 10.150	45.16 $\pm$ 10.156	50.80 $\pm$ 9.134	0.194 ^a
HAMD ₂₄ (Post)	29.11 $\pm$ 12.405	30.42 $\pm$ 10.543	43.50 $\pm$ 8.618	<0.001 ^a
HAMD ₂₄ (1 week)	23.26 $\pm$ 11.685	26.68 $\pm$ 9.563	37.15 $\pm$ 10.266	<0.001 ^a
HAMD ₂₄ (4 weeks)	22.21 $\pm$ 12.196	22.58 $\pm$ 9.353	34.80 $\pm$ 12.685	0.001 ^a
reduction (before-after) ^c	41.67% $\pm$ 0.239	29.70% $\pm$ 0.368	13.43% $\pm$ 0.151	0.006 ^a
reduction (before-1 week after) ^d	53.24% $\pm$ 0.231	37.72% $\pm$ 0.350	27.00% $\pm$ 0.162	0.010 ^a
reduction (before-4 weeks after) ^e	55.47% $\pm$ 0.219	47.17% $\pm$ 0.333	32.49% $\pm$ 0.211	0.025 ^a

SD, Standard Deviation; HAMD24, Hamilton Depression Scales-24.

^aThe *p* value for one-way ANOVA.

^bThe *p* value for Chi-square test.

^cReduction rate of HAMD24 scores for before and after treatment = ((pre-post)/pre).

^dReduction rate of HAMD24 scores for before and 1 week after treatment = ((pre-1 week)/pre).

^eReduction rate of HAMD24 scores for before and 4 weeks after treatment = ((pre-4 weeks)/pre).

differences to reduce the probability of type I error. (3) The brain regions with cluster voxels size greater than 40 were selected.

2.7 Visualization

The REST V1.8 software¹ (37) and BrainNet Viewer² (38) were used to visualize the results of brain activity and networks.

3 Results

A total of 60 participants were enrolled, but 2 subjects did not complete the full treatment course. Finally, 58 patients (46 females and 12 males, aged 18–56 years) had received 5-day treatment and 4-week follow-up. All included subjects, who were matched for gender, age, and education level, were randomly divided into three groups as follows by computer randomization sequences: the dual target group (dual group) (19 subjects, aged 27.58 $\pm$ 9.605 years), single target group (single group) (19 subjects, aged 26.32 $\pm$ 8.845 years) and sham stimulus group (sham group) (20 subjects, aged 28.70 $\pm$ 10.887 years) (Table 1).

3.1 HAMD24 analysis

At baseline, the HAMD24 scores in the dual, single, and sham groups were not significantly different (*p* > 0.05). After 5 days of aTMS treatment, the HAMD24 scores were reduced in these three groups. Additionally, this decrease persisted at 1 week and even 4 weeks after aTMS treatment. After the treatment, the reduction rates in HAMD24 scores in dual, single and sham group were 41.67% $\pm$ 0.239, 29.70% $\pm$ 0.368 and 13.43% $\pm$ 0.151, respectively. At 1 week after treatment, the rate were decreased by

53.24% $\pm$ 0.231, 37.72% $\pm$ 0.350 and 27.00% $\pm$ 0.162, respectively. At 4 weeks after treatment, the rates were decreased by 55.47% $\pm$ 0.219, 47.17% $\pm$ 0.333 and 32.49% $\pm$ 0.211, respectively. These reduction rates of HAMD24 scores in three groups were significant different (*p* < 0.05). Additionally, the reduction rate was faster and greater in the dual group than in the other two groups (Table 1, Figure 1).

3.2 ALFF and fALFF analysis

After comparing the post- and pre-TMS images by the paired *t*-test, the ALFF value in the right fusiform gyrus (FG) (peak MNI coordinate: 33, −78, −18) of the dual group was found to decrease after aTMS. Additionally, the left superior temporal gyrus (STG) (peak MNI coordinate: −57, −36, 6) in the dual group had a lower fALFF value after aTMS. In both the single and sham groups, there were no significant changes in ALFF and fALFF values in the whole brain before and after aTMS (Table 2, Figures 2A,B, 3A,B).

3.3 ROI analysis

The peak MNI coordinates for the ALFF and fALFF values (33, −78, −18 and −57, −36, 6) were selected as ROIs to explore the FC between these two ROIs with whole brain. We found that in the dual group, after 5 days of aTMS treatment, the FC between ROI1 (33, −78, −18) and the right middle frontal gyrus (MFG), left MFG, left triangular part of inferior frontal gyrus (IFG) decreased. There was no significant difference in the FC between ROI2 (−57, −36, 6) and the other brain regions before and after treatment (Table 2, Figures 2C, 3C–E).

3.4 Correlation analysis

The fALFF value of the left STG at baseline in the dual group was negatively correlated with the difference between HAMD24 scores

1 <http://www.restfmri.net>

2 <http://www.nitrc.org/projects/bnv/>

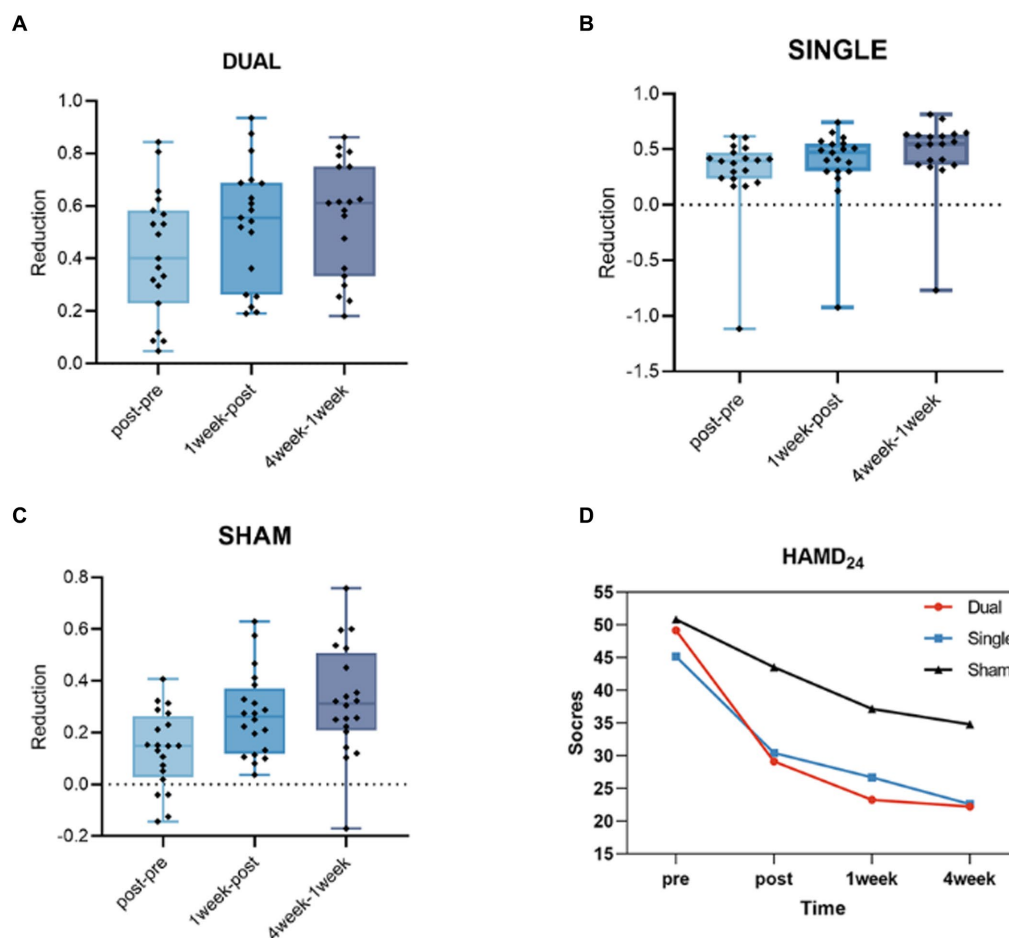


FIGURE 1

(A) The HAMD24 reduction rate from post- to pre-treatment, 1 week after treatment to post-treatment and 4 weeks after treatment to 1 week after treatment in the dual group. (B) The HAMD24 reduction rate from post- to pre-treatment, 1 week after treatment to post-treatment and 4 weeks after treatment to 1 week after treatment in the single group. (C) The HAMD24 reduction rate from post- to pre-treatment, 1 week after treatment to post-treatment and 4 weeks after treatment to 1 week after treatment in the sham group. (D) The average HAMD24 scores of pre-treatment, post-treatment, 1 week and 4 weeks after treatment in dual, single and sham groups.

before and after treatment (Δ HAMD24 score) ($r = -0.455$, $p = 0.050$, Pearson correlation), and the ALFF value of the right FG was not significantly correlated with Δ HAMD24 score (Figure 4).

4 Discussion

The current study investigated the features of spontaneous brain activity in TRD pre- and post-aTMS treatment at different targets using rs-fMRI. Specifically, we researched the efficacy and safety of aTMS for TRD by performing bilateral, unilateral, or sham stimulation at left DLPFC and right OFC and then analyzed the ALFF, fALFF and FC values of different brain regions in those three groups before and after aTMS treatment.

The DLPFC is a key region of the executive control network (ECN) that is associated with the regulation of attention, decision-making, working memory, and cognitive control. Therefore, researchers believe that applying high-frequency stimulation to the left DLPFC could help reduce depressive symptoms and further improve the mood of patients with depression (39). Additionally, the

OFC is also associated with emotions since it is reacting to reward values (40–42). A series of studies found that the OFC is a vital brain area for reward and is activated by unpleasant aversive stimuli. After the aTMS at these two targets, the depressive symptoms of TRD patients get significantly improved. These regions thus could be the strong candidate targets for stimulation to treat depression, particularly for the patients with TRD (43–46). Specifically, we found that both dual and single target stimulation reduced HAMD24 scores in the short term, indicating that both these two schemes of aTMS treatment can improve the symptoms of patients with TRD. Because the TMS could produce a strong magnetic field with repeated pulses that passes through the scalp and skull beneath the coil to enhance or weaken activity in corresponding brain area by different models of stimulation. According to the differences of frequencies, TMS stimulations are divided into low-frequency stimulation (≤ 1 Hz) and high-frequency stimulation (> 5 Hz) (47). The former and continuous theta burst stimulation (cTBS) or the latter and intermittent theta burst stimulation (iTBS) respectively execute inhibitory or excitatory effects on the brain cortex. An increasing number of related studies have also proven the effectiveness of TMS for depression. Such as a

TABLE 2 Brain regions alterations of ALFF, fALFF, and FC in TRD patients after arTMS in dual group.*

Brain regions	Left/Right	Peak MNI coordinate			Clusters (voxel)	Peak T value
		x	y	z		
Post < hoc						
ALFF						
Fusiform Gyrus ^a	R	33	-78	-18	41	-5.5831
fALFF						
Superior Temporal Gyrus ^b	L	-57	-36	6	42	-6.4519
FC of seed1: right fusiform gyrus (Peak MNI: 33-78 -18)						
Middle Frontal Gyrus ^c	R	36	21	39	71	-4.7969
Middle frontal gyrus ^c	L	-39	15	57	59	-6.3005
Inferior frontal gyrus, triangular part ^c	L	-51	21	24	52	-5.8810
FC of seed2: left superior temporal gyrus (Peak MNI: -57 -36 6)						
NONE						

ALFF, Low-frequency Fluctuation; fALFF, Fractional Amplitude of Low-frequency Fluctuations. FC, Functional Connectivity. MNI, Montreal Neurological Institute. HAMD24, Hamilton Depression Scale-24. The peak MNI coordinate represent the peak points with most significant differences in the brain areas. Gaussian Random Field (GRF) correction: voxel *p* value = 0.002, cluster *p* value = 0.1, two tail (*Z* > 2.3, cluster *p* = 0.05, one tail).
*There was no significant result in both single and sham group after the GRF correction.
^aThe result of ALFF analysis.
^bThe result of fALFF analysis.
^cThe result of ROI analysis with the seed of right Fusiform Gyrus.

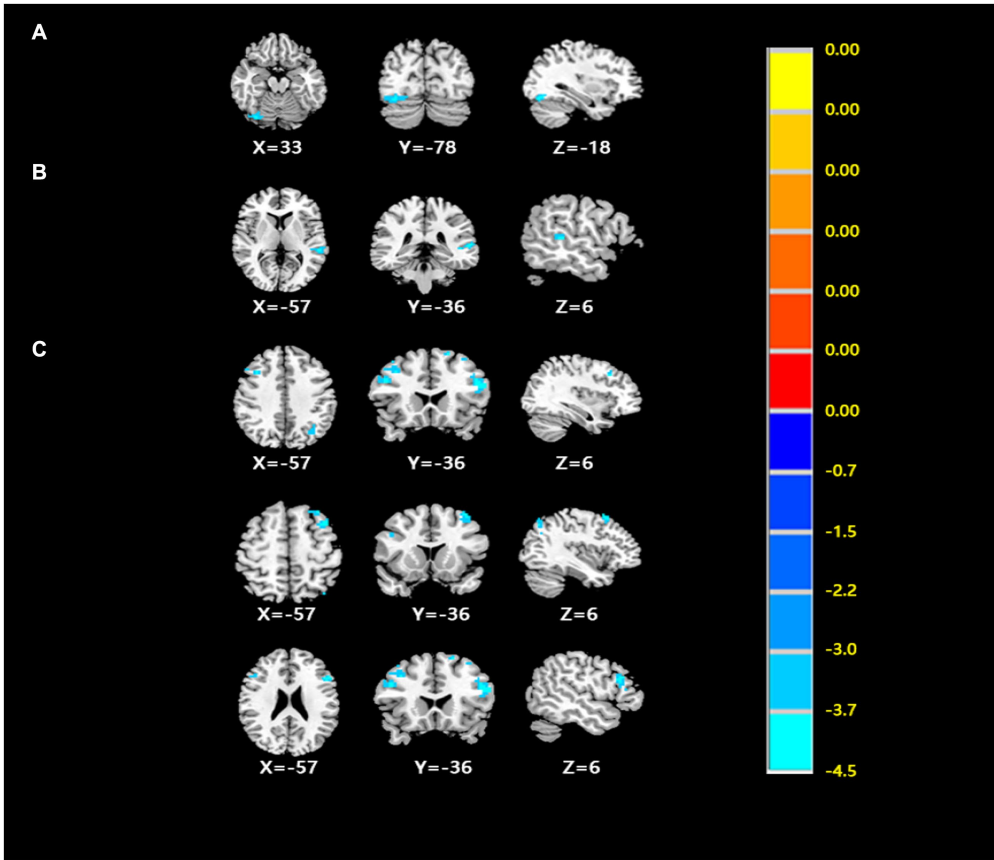


FIGURE 2
(A) The differences of ALFF from post- to pre- treatment in the dual group. (B) The differences of fALFF from post- to pre- treatment in the dual group. (C) The differences of FC from post- to pre- treatment in the dual group. (Cluster *p* < 0.05, GRF corrected) (Cluster *p* < 0.05, GRF corrected).

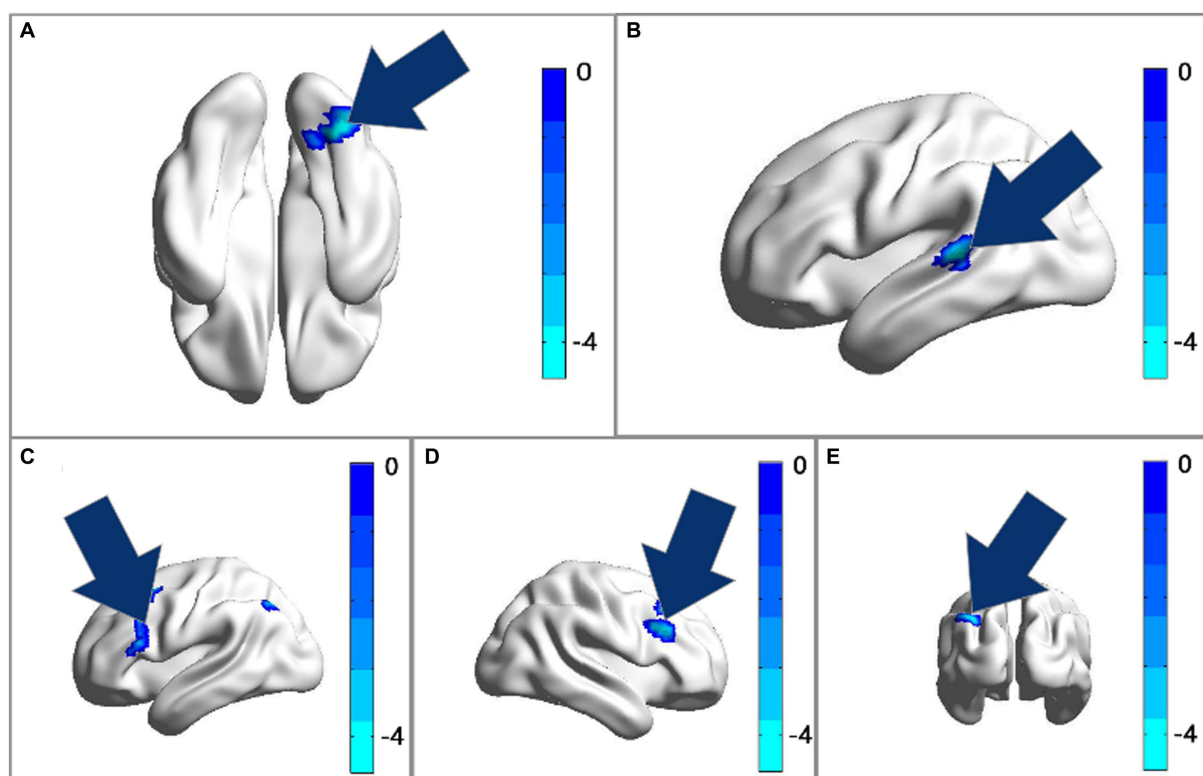


FIGURE 3

(A) The ALFF analysis revealed significant reductions in the right fusiform gyrus after treatment. (B) The fALFF analysis revealed significant reductions in the left superior temporal gyrus after treatment with GRF correction. (C–E) The FC of ROI1 (33, -78, -18) with the bilateral middle frontal gyrus and triangular part of inferior frontal gyrus had decreased after treatment. Cool colors represent decreased value, while warm colors represent increased value. These differences were obtained by paired t-test in the dual group.

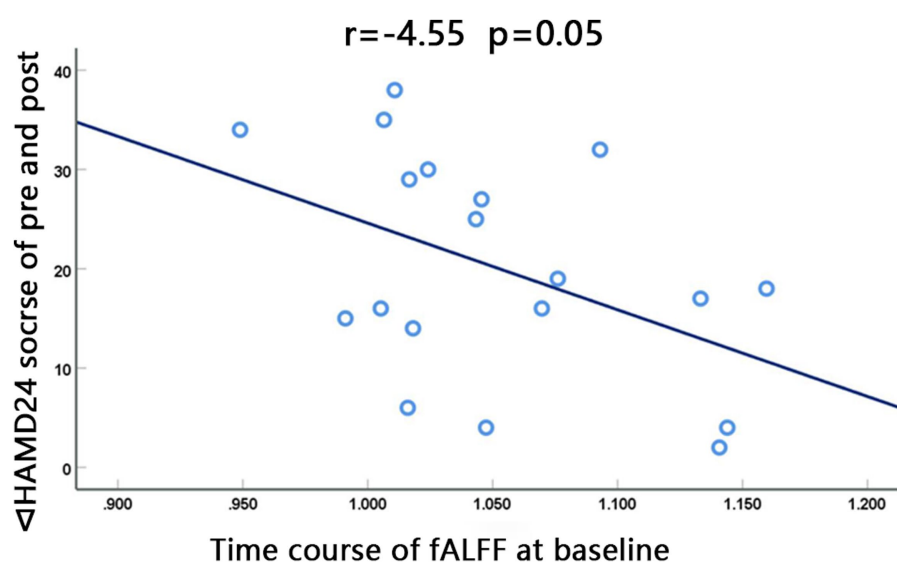


FIGURE 4

The fALFF value at baseline of the left superior gyrus in the dual group was negatively correlated with the difference between HAMD₂₄ scores before and after treatment (Δ HAMD₂₄ score). ($r = -0.455$, $p = 0.050$, Pearson correlation).

meta-analysis (48) that included 15 published articles on the use of repetitive transcranial magnetic stimulation (rTMS) to treat depression from 2001 to 2010 concluded that compared with sham

stimulation, real rTMS targeting the left and right DLPFC with high- and low-frequency stimulation was effective in the treatment of depression. Besides, a recent study showed that the response rates to

rTMS of patients with major depressive disorder (MDD) were 40 to 50%, and the remission rates were 25 to 30% (49). In our study, the dual group showed a faster and greater decrease than the single and sham group. In addition, after dual target stimulation, at 1 week after the treatment and at 4 weeks after the treatment, the reduction rates in HAMD24 scores were also increasingly greater in the dual group than that in the other two groups. Importantly, both dual and single target stimulation showed good safety and tolerability. In this study, none of the subjects experienced adverse reactions, such as severe headache, seizures, or hearing loss, during treatment.

Additionally, we used the ALFF to observe the fluctuation of the average amplitude of voxels in the frequency range of 0.01–0.08 Hz; this value directly indicates changes in the amplitude of the BOLD signal and reflects the spontaneous activity of brain regions (28). In this study, we found that after dual target aTMS, the ALFF value of the right FG was significantly lower than that before treatment. This finding is consistent with the results of a previous rs-fMRI study that revealed patients with depression tend to be with higher ALFF values in the right FG (50). Numerous rs-fMRI studies have found that changes in the FG of patients with depression suggested that the neurological activity of this brain region is altered, which may be the basis of depression (51–53). As well known, the FG is a part of the visual recognition network and temporal cortex, which is at the same time responsible for facial recognition and the deep processing of visual information as well as negative cognition and emotion. So, it may be the area to display the earliest signs of abnormal emotional processing in patients with depression (54–56). Besides, abnormal spontaneous brain activity of the FG may indicate impaired understanding and memory of language as well as recognition of facial features in MDD patients, which may lead to negative cognition and affect in both learning and life (57).

We also found that after aTMS treatment the FC of the right FG was decreased. Specifically, the FC between the right FG and bilateral MFG and left triangular part of IFG was decreased after treatment. Shan et al. also found that the FC of the right FG was abnormal in patients with depression, which may produce mood disorders (58, 59). And this kind of abnormal FC of right FG mainly focused on the frontal lobe which could divide into the supra, middle, and lower folds (60). Because it is one of the areas involved in the higher functional activities of the human brain, influencing social behavior, planning, language formation, working memory, language search, extraction, naming and other functional activities, it is closely related to many mental diseases. In addition, a study by Liu et al. also suggested that spontaneous brain activity in the right MFG of patients with depression is significantly correlated with depressive symptoms (61). One of our previous studies also indicated that the changed of the FC between right preacuneus and MFG was related to improvement of depressive symptoms after cognitive-behavioral therapy combined with drugs (62). The MFG is a core area of the DLPFC, which plays a key role in emotional supervision and cognitive processing (63). Hyperactivities in this area was observed in depressive patients compared to controls (64). As a part of DLPFC, the left IFG is extensively involved in language processing, working memory and cognitive control (65–68). When the processing of negative emotions increases, it can specifically inhibit the overworked

limbic system by connecting with the orbitofrontal cortex, so that negative emotion processing is reduced (69). Conversely, when the processing of negative emotions is reduced, the functional connectivity between these two brains decreases.

The fALFF, obtained by dividing the energy of the low-frequency signal by the energy of the entire frequency band, is a common indicator of resting-state fMRI and can reduce the influence of noise in the data (70). Hence, in this study, we also used fALFF to observe the effective reduction of the intensity of spontaneous neuronal activity in brain regions. Related studies found that the fALFF of the left STG in patients with depression was significantly increased (71, 72). After aTMS, we found that the fALFF of the left STG, decreased compared to that at baseline in the dual group, which is consistent with the results of other studies (73, 74). Moreover, fALFF value of the left STG at baseline in the dual group was negatively correlated with the Δ HAMD24 score before and after treatment. Some fMRI studies also have showed alterations in the STG in patients with depression (73, 74). The STG is a critical part of temporal lobe which is mainly responsible for not only processing auditory information but also advanced neural activities such as social cognition (75). Some studies have found that the STG and its adjacent cerebral cortex played an important role in processing information related to individual communication (such as eye gaze direction, facial expression, and lip movements). Thus, it may be mainly responsible for the dynamic processing of facial features, which is more important during individual communication (76).

The STG and FG, as part of the temporal-occipital junction, were reported to be more sensitive to negative emotional information (77). And after this kind of protocol of aTMS treatment, it took a short period to improve the abnormal ALFF values and FC in FG as well as abnormal fALFF valued in STG and then to reduce this sensitivity, thereby helping to improve the negative mood of patients with TRD.

5 Conclusion

This study has demonstrated that the efficacy of the dual target treatment was better than that of the single-target and sham treatments. In addition, we also demonstrated that the functional disorder of the right FG and left STG, which could be significantly improved after aTMS treatment, may be the pathological bases of emotional and cognitive disorder in depression. And these areas may indicate the potential marker of efficacy of dual target aTMS treatment. Particularly, higher baseline fALFF values in the left STG may suggest better response for dual target aTMS treatment. These findings may help improve the understanding of neurobiological mechanism of TRD.

6 Limitations and future directions

This study has the following limitations: firstly, the sample size is small which should be further expanded in future studies. Secondly, a precise navigation system was not used. This may result in some errors due to insufficient anatomical data support and failure to consider individual differences. Thirdly, it wasn't made an assessment of what might be a protective factor through psychotherapy and counseling intervention during the survey. In future research, we will further improve these shortcomings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Second People's Hospital of Guizhou. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JL: Formal analysis, Methodology, Visualization, Writing – original draft. YS: Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing. GW: Methodology, Project administration, Resources, Supervision, Writing – review & editing. LH: Investigation, Methodology, Writing – review & editing. HC: Investigation, Methodology, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Regional decreases of cortical thickness in major depressive disorder and their correlation with illness duration: a case-control study

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Background: Alterations in brain structure and function in major depressive disorder (MDD) have been identified in a number of studies, but findings regarding cortical thickness were various and inconsistent. Our current study aims to explore the differences in cortical thickness between individuals with MDD and healthy controls (HC) in a Chinese population.

Methods: We investigated T1-weighted brain magnetic resonance imaging data from 61 participants (31 MDD and 30 HC). The cortical thickness between the two groups and analyzed correlations between cortical thickness and demographic variables in the MDD group for regions with significant between-group differences were conducted.

Results: Compared with the HC group, patients with MDD had significantly decreased cortical thickness, in left pars triangularis, left pars orbitalis, left rostral middle frontal gyrus, left supramarginal gyrus, right parahippocampal gyrus, right lingual gyrus, right fusiform and right inferior parietal gyrus. The cortical thickness of left rostral middle frontal gyrus was negatively correlated ($r = -0.47$, $p = 0.028$) with the illness duration in patients with MDD.

Conclusion: Our study distinguished that cortical thickness decreases in numerous brain regions both in the left and right hemisphere in individuals with MDD, and the negative correlation between the cortical thickness of left rostral middle frontal gyrus illness duration. Our current findings are valuable in providing neural markers to identify MDD and understanding the potential pathophysiology of mood disorders.

KEYWORDS

cortical thickness, major depressive disorder, left supramarginal gyrus, brain magnetic resonance imaging, T1

1 Introduction

Major depressive disorder (MDD) is becoming the most burdensome mental disorder globally. The illness involves a depressed mood or loss of pleasure or interest in activities for long periods of time (1). Many alterations of behavioral symptoms are involved during the development process of MDD, including various fields related to emotions, motivation, cognition, and physiology (2). Although ongoing efforts to increase knowledge and skills for healthcare providers and clinical researchers, the pathogenies and pathophysiological processes of MDD are not fully understood (3). The existing evidence suggests that MDD may involve multiple levels of changes in genetics, biochemistry, imaging, and psychology. Due to neuroimaging research can reflect changes in the brain structure and function of MDD patients more intuitively, increasing studies are using this technology to explore the pathological mechanisms of MDD.

Cortical thickness refers to the component of gray matter volume, which is an index of cell density and health in the cerebral cortex (4). Thus, the alteration of cortical thickness represents an important signature for understanding emotional regulation of depression among all the neuroimaging approaches. For example, region-wise analysis reported that abnormal changes in the cortical thickness of the limbic system, such as the orbitofrontal lobe, cingulate gyrus, and other brain regions in untreated individuals with MDD, which may be related to abnormal emotional management and known as frontal limbic model of MDD (5). Temporal cortical thickness abnormalities were also reported in mood disorders (6). Two meta-analyses found that decreased cortical thickness in the orbitofrontal and temporal cortex of MDD (7, 8). A pilot study reported antidepressant treatment increased cortical thickness of the left medial OFC in adolescents with major depression (9). Several studies have also pointed out the increases in cortical thickness of specific brain regions in MDD. Qiu and colleagues reported cortical thickness in the right hemisphere in first-episode, treatment-naïve, mid-life MDD patients (10). Increased cortical thickness of several brain regions in the default mode network (DMN) of individuals with MDD was also reported in the meta-analysis (7). Specifically, Li et al. found that increased cortical thickness of posterior cingulate cortex, right ventromedial prefrontal cortex, and anterior cingulate cortex, and decreased cortical thickness in orbitofrontal cortex (gyrus rectus and orbital segment of superior frontal gyrus) and temporal cortex in medication-free patients with MDD.

Thus, to date, the existing studies related to cortical thickness in individuals with MDD are not well clarified. Results have been somewhat inconsistent across different studies. Our current study aims to explore the differences in cortical thickness of individuals with MDD and healthy controls in a Chinese population. According to the previous evidence, we hypothesize that the individuals with MDD will have thinner cortices in the frontal, temporal, limbic system, and parietal lobes (e.g., middle frontal gyrus and orbitofrontal cortex).

2 Methods

2.1 Ethical approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and

institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Medical Ethics Committee of Zhumadian Second People's Hospital in Henan Province (Approval no. IRB-2020-006-02). All participants provided written informed consent prior to participation.

2.2 Participants

All participants of this study were recruited from Zhumadian Second People's Hospital in Henan Province. A total of 30 individuals diagnosed with MDD and 31 age and sex-matched healthy controls were included in the data analysis. All patients with MDD were recruited during a depressive episode, which were diagnosed by two professional and experienced psychiatrists. The inclusion criteria for MDD are as follows: (1) individuals meeting the diagnosis of major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5); (2) Hamilton Depression Scale (HAMD)-24-item version scores ≥ 20 ; (3) the patients taking medication were on a stable dose for at least 6 weeks or were unmedicated for at least 4 weeks; (4) 18–60 years old without gender not limited; and (5) primary school or above education level. The healthy controls had no history of mental illness or severe physical illness and no family history of mental illness. The exclusion criteria of all participants were as follows: (1) any history of neurological diseases, intellectual disability, other physical diseases, or comorbidities of other disorders; (2) any other mental disorders; (3) pregnancy or breastfeeding; and (4) head trauma resulting in loss of consciousness. The basic information of all participants can be seen in Table 1. There were only twenty-two patients with MDD having the illness duration, and eighteen patients having body mass index scores.

2.3 Image acquisition

The structural T1 images of all participants were scanned by using the 3D BRAVO with the following parameters: TR/TE = 6.77/2.49 ms, flip angle = 7°, matrix size = 256 × 256, voxel size = 1 × 1 × 1 mm³, 188 slices.

TABLE 1 Demographic information of participants.

Variable	MDD (n = 30)	HC (n = 31)	p-value
Age (years, mean ± SD)	35.67 ± 9.47	36.53 ± 9.21	0.720
Gender (female/male)	17/13	18/13	0.912
Illness duration (months, mean ± SD)	35.55 ± 47.81	–	–
Body mass index (kg/m ² , mean ± SD)	22.63 ± 2.82	–	–

MDD, major depressive disorder; HC, healthy control; SD, standard deviation.

2.4 Preprocessing of T1 images

The T1 images were automatically preprocessed using the Computational Anatomy Toolbox version r1932.¹ Briefly, the bias field correction was firstly performed for the T1 images, which were then segmented into gray matter, white matter and CSF. After removing brain stem and cerebellum, the cortical thickness was computed by using a projection scheme (11), which resulted in individual cortical thickness maps. This projection-based thickness estimation is fast and robust, which has been applied in other studies of neuropsychiatric disorders (12, 13). The individual maps of cortical thickness cannot be compared because they have a different number of vertexes. Thus, those maps were then warped and registered to standard space (fsaverage), thus, enabling matching of cortical locations among individuals across the whole surface. The registered cortical thickness maps were then smoothed with 12 mm full width at half maximum for statistical analysis.

2.5 Statistical analysis

The differences in gender and age between patients with MDD and HC were performed by using the chi-square test and two-sample *t*-test separately. The two-tailed two-sample *t*-test was also used to investigate the difference in cortical thickness at the vertex level between MDD patients and HC. The multiple comparisons were corrected using the false discovery rate (FDR) with $q < 0.05$.

If there were some brain areas that survived the FDR correction, mean cortical thickness of those brain areas was extracted for patients with MDD, and was used to compute the association with illness duration and body mass index by using Pearson correlation analysis. The statistical level of $p < 0.05$ was considered significant.

3 Results

The basic information of included participants is shown in Table 1. The average age of MDD group and HC group are 35.67 ± 9.47 years old and 36.53 ± 9.21 , respectively. In total, seventeen females and thirteen males were included in the MDD group, and eighteen females and thirteen males were included in HC group. There was no significant difference ($p > 0.05$) in age and gender between patients with MDD and HC.

A two-sample *t*-test revealed that patients with MDD had significantly (FDR with $q < 0.05$) decreased cortical thickness, compared with HC, in left pars triangularis, left pars orbitalis, left rostral middle frontal gyrus, left supramarginal gyrus, right parahippocampal gyrus, right lingual gyrus, right fusiform and right inferior parietal gyrus (Figure 1 and Table 2). There were no brain areas showing increased cortical thickness in patients with MDD.

In addition, we found that the cortical thickness of left rostral middle frontal gyrus was negatively correlated ($r = -0.47$, $p = 0.028$) with the illness duration in patients with MDD (Figure 2). We conducted a sensitivity analysis to explore the relationship

between the course of the disease and cortical thickness after excluding a value of very long illness duration, and the results showed that the difference was still statistically significant ($r = -0.43$, $p = 0.047$, Supplementary Figure S1). We did not find significant correlation between cortical thickness of those brain areas and body mass index.

4 Discussion

By utilizing T1 weighted anatomical magnetic resonance imaging (MRI) images, we investigated the changes in cortical thickness in individuals with MDD. The main findings of current study are as follows: (1) four left hemisphere brain regions (i.e., pars triangularis, pars orbitalis, rostral middle frontal gyrus, and supramarginal gyrus) were found to have thinner cortical thickness in individuals with MDD when compared to HC; (2) the decreases in cortical thickness of three right hemisphere brain regions (i.e., parahippocampal gyrus, lingual gyrus, fusiform, and inferior parietal gyrus) was also reported in MDD; and (3) the cortical thickness of left rostral middle frontal gyrus was negatively correlated with the illness duration in individuals with MDD. The results reported in our study provided new evidence for exploring alterations in the brain structure of MDD.

Consistent with the abnormal cortical thickness observed in previous studies, we observed a decrease in cortical thickness in several regions of the left hemisphere of the brain. It is worth noting that we have found that left rostral middle frontal gyrus was negatively correlated with the illness duration in individuals with MDD. The rostral middle frontal gyrus is partly located in dorsolateral prefrontal cortex and the control network of brain (14), and it plays an important role in dysfunctional emotional processing, frontal executive function, working memory, and problem solving (14). Consistent with our results, a study focused on the thickness and depression reported that the cortical thickness of rostral middle frontal gyrus was negatively related to positive emotions at small effect sizes (accounting for 0.2–2.4% of variance; p -fdr: 0.0051–0.1900) (15). Song and colleagues reported that left rostral middle frontal gyrus thickness was negatively correlated with genetic risk score at 0.05 threshold (corrected $p < 0.05$), and mediates the relationship between genetic risk and neuroticism traits (16). Another study focused on the brain imaging of bipolar disorder also found significantly thinned left rostral middle frontal gyrus in individuals with patients when compared with the healthy controls ($d = -0.276$; $p = 2.99 \times 10^{-19}$) (17). Our findings and the above evidence suggested that left rostral middle frontal gyrus is a potential hallmark to distinguish mood disorders, and may be negatively correlated to the positive emotions, genetic risk score and illness duration of depression. However, some studies have proposed inconsistent views. Qiu et al. and van Eijndhoven et al. reported increased cortical thickness in right rostral middle frontal gyrus in first-episode, medication-free MDD patients (5, 10). Reynolds and colleagues found both right and left rostral middle frontal gyrus were thicker in youth with MDD than in controls ($p = 0.009$; Left – controls: 2.74 ± 0.28 , MDD: 2.94 ± 0.25 ; Right – controls: 2.77 ± 0.26 , MDD: 2.80 ± 0.28) (18). Thus, characteristics of rostral middle frontal gyrus in MDD patients can be explored through meta-analysis, and it is also worthy of further confirmation by large samples.

Left pars triangularis is located in ventrolateral prefrontal cortex, and it has been reported to be related to cognitive control (19). Consistent with our findings, a case-control study also reported

¹ <https://neuro-jena.github.io/cat/>

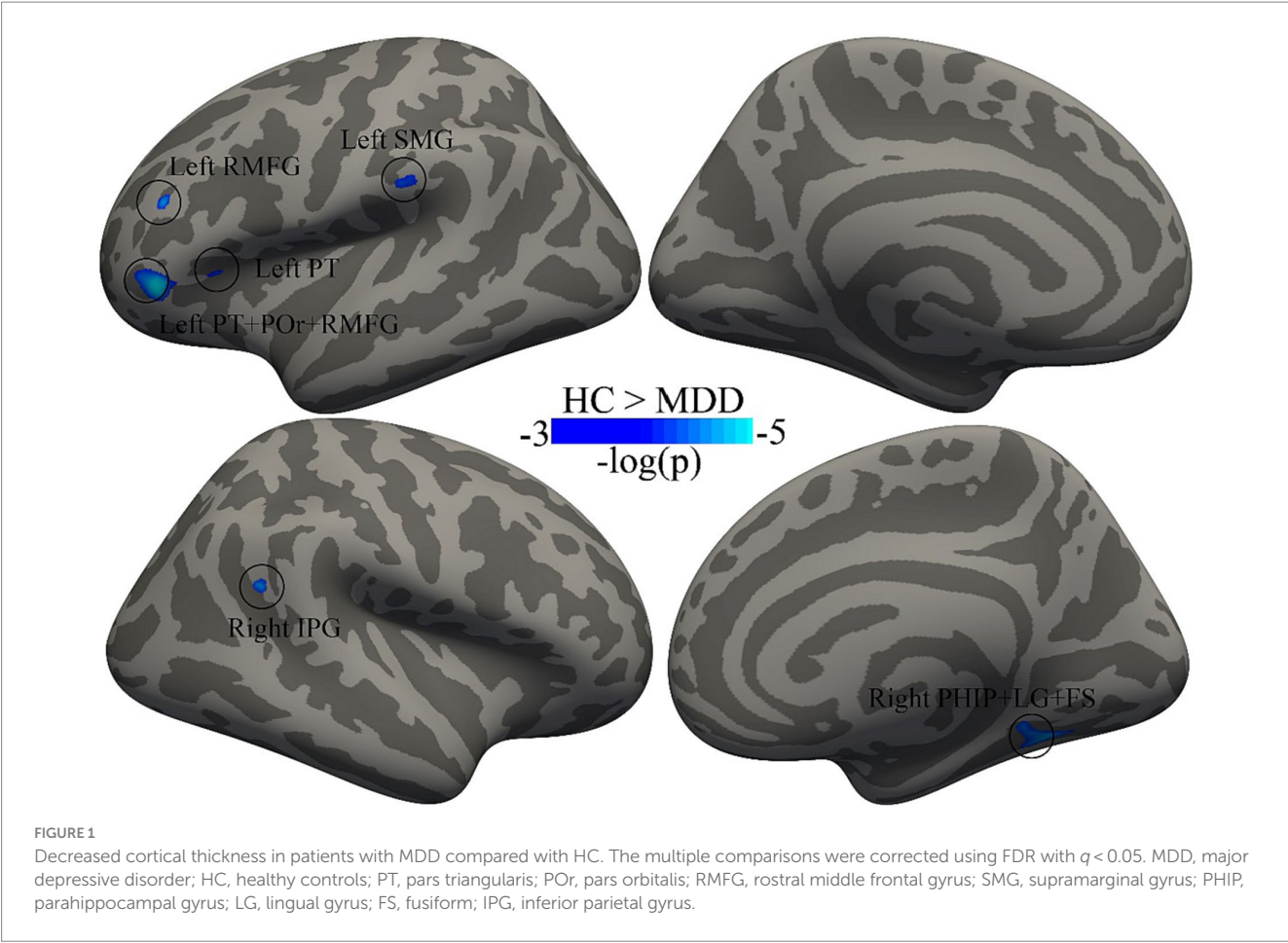


TABLE 2 Brain areas where the cortical thickness was significantly decreased in patients with MDD.

Brain regions	Number of vertex	Cluster size (mm ²)	MNI coordinate			t-value	Effect size (Cohen's d)
			X	Y	Z		
Left PT+ POr+ RMFG	390	231.09	-47	36	-4	-4.76	1.22
Left RMFG	59	32.08	-41	35	22	-2.43	0.62
Left SMG	94	41.83	-61	-28	22	-4.16	1.07
Left PT	35	12.40	-34	26	8	-4.1	1.05
Right PHIP+ LG+ FS	394	209.2	33	-56	-8	-4.51	1.16
Right IPG	73	29.41	50	-47	22	-4.36	1.12

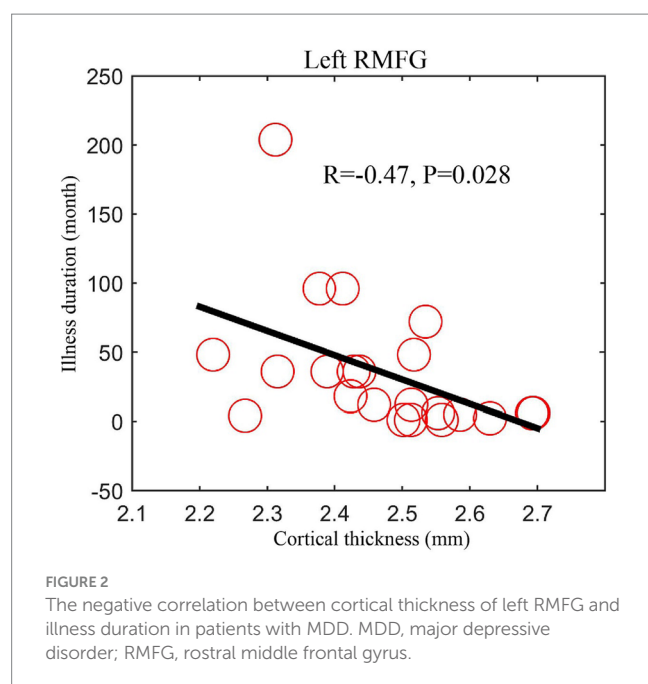
MDD, major depressive disorder; PT, pars triangularis; POr, pars orbitalis; RMFG, rostral middle frontal gyrus; SMG, supramarginal gyrus; PHIP, parahippocampal gyrus; LG, lingual gyrus; FS, fusiform; IPG, inferior parietal gyrus.

thinner cortical thickness of left pars triangularis in MDD group when compared with HC group (20). Functional MRI data analysis with a semantic task indicated that left inferior frontal cortex (pars triangularis) contributed to the classification of depression and controls (21).

We also found a joint region of left pars triangularis+ pars orbitalis+rostral middle frontal gyrus had a decrease in cortical thickness in individuals with MDD. Similar to pars triangularis, pars orbitalis also plays important roles in the language production network (22). We did not find much evidence to focus on changes in the pars orbitalis brain region and its function in MDD. A brain structure study with children and adolescents suggests that it may

be higher impulsivity, but not depressive symptoms, was associated with reduced cortical thickness in the pars orbitalis (23). Moreover, the cortical thickness of left supramarginal gyrus was inconsistently reported in previous studies (4, 10, 24, 25). The potential roles of left supramarginal gyrus in MDD also need to be further clarified.

Regarding the brain regions mentioned in the right hemisphere with cortical thickness decreases in our results, to the best of our knowledge, previous studies have focused more on exploring changes in their functional connections. For example, a case-control study reported late-life depression exhibited lower intrinsic functional connectivity in right inferior parietal gyrus and other right fronto-parietal network (FPN) (26). However, another study included 25



patients with recurrent depression found functional connectivity was considerably decreased in right inferior parietal gyrus after 8 weeks treatment (27). Few studies have pointed out the causes and rules of the structural and functional changes of right inferior parietal gyrus in patients with depression. The existing evidence suggests that right inferior parietal gyrus might be a crucial hub in transferring information between these abnormal regions (26).

Our results also reported a decrease in cortical thickness of the occipito-temporal cluster (i.e., right parahippocampal gyrus+ lingual gyrus+ fusiform) in MDD. Similarly, a study with an overlapping twin and sibling sample reported the reduction of surface area in an occipito-temporal cluster, which comprised part of the right lingual, fusiform and parahippocampal gyri (28). The decrease of cortical thickness the right fusiform in MDD cases with comorbid generalized anxiety were also reported previously (29). The meta-analysis by the ENIGMA-MDD group also found a significant reduction of right lingual gyrus surface area, but nonsignificant association for fusiform or parahippocampal, in adolescent depression (30). Previous evidence pointed out the reduced cortical thickness of occipito-temporal cluster may be associated with visual memory and attention deficits in depression (31). The right lingual gyrus may be associated with cognitive functions in MDD. The evidence from ENIGMA-MDD group and other studies points to differences in orbitofrontal and cingulate cortices between MDD and healthy controls (30, 32). However, our study did not provide such evidence, which is not surprising. This may be due to the significant heterogeneity in both clinical manifestations and brain structure among patients with MDD. The underlying reasons for the structural and functional alterations of these brain regions deserve further exploration.

The current study demonstrated a decrease in cortical thickness in several brain regions of individuals with MDD in a Chinese population, which provides new evidence for the neuroimaging approaches to mood disorders. However, several limitations should be noted in the present psychiatric neuroimaging study. Firstly, our study is based on a single institutional database, a certain degree of

selection bias may limit our extrapolation of results. Secondly, the information on BMI was only collected in MDD group, while the medication records of patients were not available from our collected data. The evidence from ENIGMA-MDD group reported obesity (BMI > 30) was significantly associated with both mass univariate and multivariate pattern recognition analyses independent of MDD diagnostics (33). Their results suggested a neurobiological interaction between obesity and brain structure under physiological and pathological brain conditions. Thus, obesity may affects the brain just as much as a neuropsychiatric condition would and should be treated taking this into account. However, our study did not find association between BMI and with brain cortical thickness in MDD. We think this may be related to our small sample size and limited number of overweight and obese individuals in current study. In our study sample, only 8 out of all 30 depressed patients met the criteria for overweight, and no study subjects met the criteria for obesity. Since the BMI of our study subjects is generally within the normal range, it may require more individuals with ultra-high BMI to determine alterations in brain cortical thickness. Thirdly, our study is a cross-sectional study, so we cannot determine whether the brain structure of MDD undergoes changes after treatment.

Moreover, our sample consists of first-episode and recurrent patients, we cannot exclude the potential influence of the previous treatment effects and their influence on reported findings. Additionally, we did not control for other information, such as maternal status, professional activity, and manual laterality, and we also did not control that the research subject must be right-handed. These variables should be considered in future studies. Many residue confounders might as well affect the findings of the study. Larger samples and longitudinal research are needed to explore whether the decrease in cortical thickness in MDD patients can be improved through drug treatment in the future.

5 Conclusion

Our findings serve as a supplement to the evidence of alterations in cortical thickness among individuals with MDD in the Chinese population. In summary, our study distinguished that cortical thickness decreases in numerous brain regions (i.e., pars triangularis, pars orbitalis, rostral middle frontal gyrus, and supramarginal gyrus of the left hemisphere; and parahippocampal gyrus, lingual gyrus, fusiform, and inferior parietal gyrus of the right hemisphere) in individuals with MDD. Moreover, the cortical thickness of left rostral middle frontal gyrus was negatively correlated with the illness duration of the disorder. Our current findings are valuable in providing neural markers to identify MDD, which contribute to the clinical diagnosis of affective disorders and further improve our understanding of the potential pathophysiology of MDD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Medical Ethics Committee of Zhumadian Second People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CZ: Formal analysis, Investigation, Methodology, Writing – original draft. BM: Formal analysis, Writing – original draft, Software. XH: Writing – original draft, Methodology, Writing – review & editing. XG: Writing – review & editing, Supervision. FW: Writing – review & editing, Conceptualization. HG: Supervision, Writing – review & editing. JZ: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2024.1297204/full#supplementary-material>

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Manifold alteration between major depressive disorder and healthy control subjects using dynamic mode decomposition in resting-state fMRI data

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Background: The World Health Organization has reported that approximately 300 million individuals suffer from the mood disorder known as MDD. Non-invasive measurement techniques have been utilized to reveal the mechanism of MDD, with rsfMRI being the predominant method. The previous functional connectivity and energy landscape studies have shown the difference in the coactivation patterns between MDD and HCs. However, these studies did not consider oscillatory temporal dynamics.

Methods: In this study, the dynamic mode decomposition, a method to compute a set of coherent spatial patterns associated with the oscillation frequency and temporal decay rate, was employed to investigate the alteration of the occurrence of dynamic modes between MDD and HCs. Specifically, The BOLD signals of each subject were transformed into dynamic modes representing coherent spatial patterns and discrete-time eigenvalues to capture temporal variations using dynamic mode decomposition. All the dynamic modes were disentangled into a two-dimensional manifold using t-SNE. Density estimation and density ratio estimation were applied to the two-dimensional manifolds after the two-dimensional manifold was split based on HCs and MDD.

Results: The dynamic modes that uniquely emerged in the MDD were not observed. Instead, we have found some dynamic modes that have shown increased or reduced occurrence in MDD compared with HCs. The reduced dynamic modes were associated with the visual and saliency networks while the increased dynamic modes were associated with the default mode and sensory-motor networks.

Conclusion: To the best of our knowledge, this study showed initial evidence of the alteration of occurrence of the dynamic modes between MDD and HCs. To deepen understanding of how the alteration of the dynamic modes emerges from the structure, it is vital to investigate the relationship between the dynamic modes, cortical thickness, and surface areas.

KEYWORDS

resting-state fMRI, dynamic mode decomposition, major depressive disorder, manifold, density ratio estimation

1 Introduction

The World Health Organization has reported that approximately 300 million individuals suffer from the mood disorder known as major depressive disorder (MDD). MDD gives rise to psychological symptoms, such as despondent moods and negative cognitions, as well as physical symptoms, such as sleep disturbances and fatigue in mild cases, and even suicide in severe cases (1). Neurotransmitter reuptake inhibitors, such as selective serotonin reuptake inhibitors and transcranial magnetic stimulation through electrical stimulation, have been employed in the treatment of MDD (2–4). Although these treatments are effective, there are patients whose depressive symptoms improve only partially or not at all (5). Therefore, the mechanisms underlying MDD need to be elucidated.

Non-invasive measurement techniques have been utilized to reveal the mechanism of MDD, with resting-state functional magnetic resonance imaging (rsfMRI) being the predominant method (6). To evaluate dynamic changes in blood oxygenation level-dependent (BOLD) signals using rsfMRI, static functional connectivity (sFC), dynamic functional connectivity (dFC), and energy landscape (EL) were employed as indices to portray the dynamics of whole-brain networks. sFC captures the static relationships of spontaneous fluctuations that represent correlations over the entire duration (7, 8), whereas dFC captures time-resolved spontaneous fluctuations in which functional connectivity (FC) changes over a short time (9–11). Evaluation of the static and dynamic relationships of spontaneous fluctuations in the whole-brain network has revealed that MDD exhibits abnormal connections in FC, such as the default mode network (DMN), control executive network (CEN), and salience network (SN) when compared with healthy controls (HCs) (12–16). Analyzing sFC involves calculating the correlation between two independent regions for all pairs (17). Even if a pair of regions is not directly structurally interconnected, their sFC can exhibit a strong correlation if both regions receive input from a third region (18). Hence, it is imperative to simultaneously represent the dynamics of whole-brain networks based on neural activity across multiple regions. This is where EL emerges, which utilizes a pairwise maximum entropy model to represent the dynamics of the whole-

brain network in terms of the activity within each region and the interactions between two or more regions (19). Moreover, by defining the functional network between subjects in terms of energy, it is possible to evaluate the transition from one stable state to another through the unstable states. Notably, MDD tends to sink to specific states, and it is difficult to transition from one stable state to another compared to HCs (20). Although EL excels in stability analysis across subjects, some issues require prior assignment of a functional network to each region and binarization of BOLD signals. In common with sFC, dFC, and EL, analyzing components of the BOLD signal above 0.1 Hz is a challenging problem. Therefore, in terms of interactions across multiple regions, a methodology is required to evaluate the sinking into specific states under conditions free from functional network assignment and binarization.

The dynamic mode decomposition (DMD) is a data-driven and equation-independent approach for analyzing fluid dynamics (21). DMD calculates eigenvectors and corresponding eigenvalues of the approximate linear transformation expressing the time evolution of multidimensional time-series data. Eigenvectors were called dynamic modes (DMs) representing coherent spatial patterns and the corresponding eigenvalues were called discrete-time eigenvalues representing the frequency and time evolution such as growth and decay. In other words, multiple coherent DMs coexist at a certain time in multidimensional time-series data and corresponding temporal characteristics are identified. EL analysis assigns a functional network to each region, binarizes the BOLD signal, fits it with a Boltzmann distribution, determines relationships between activity patterns and energy, and assigns one state on EL at a certain time in multidimensional time-series data (22). Here, since the BOLD signals exhibit wave superposition, it is necessary to analyze stability under conditions where multiple states coexist at a certain time. DMD was successful and recent studies have applied DMD to BOLD signals, a type of fluid that exhibits nonlinear spatiotemporal changes (23–26). This study applied DMD to the BOLD signals across all frequency bands of HCs and MDD. Subsequently, the spatial patterns, frequencies, and temporal changes across all subjects were analyzed in terms of stability.

Analysis of a large dataset of psychiatric disorders based on rsfMRI (27) using DMD revealed that the number of DMs associated

with MDD decreased in visual networks (VN) and SN, while it increased in DMN and sensory-motor networks (SMN) when compared to HCs. Interestingly, DMs' differences between MDD and HCs were identified not only within the 0.01–0.1 Hz range in standard rsfMRI analysis but also extending beyond 0.1 Hz. Applying t-distribution stochastic neighbor embedding (t-SNE) (28) to DMs enables the disentangling of the intricate curved surfaces spanned by DMs into a two-dimensional manifold, allowing for the evaluation of stability across subjects. Subsequently, DMs resembling resting-state networks (RSNs) were identified by evaluating the probability density ratio between HCs and MDD using a two-dimensional manifold. The amplitudes of the DMs resembling the VN and SN were similar to the spatial patterns associated with cortical thickness and surface area abnormalities in MDD (29).

2 Materials and methods

In this study, we applied DMD to BOLD signals and devised a method for extracting DMs based on the probability density ratio between HCs and MDD on two-dimensional manifolds using t-SNE (Figure 1). First, the BOLD signals of each subject were transformed into DMs representing coherent spatial patterns and discrete-time eigenvalues to capture temporal variations using DMD. Second, all the DMs were disentangled into a two-dimensional manifold using t-SNE. Finally, density estimation and density ratio estimation were applied to the two-dimensional manifolds after the two-dimensional manifold was split based on the HCs and MDD. The results revealed that MDD tended to sink into specific DMs in contrast to HCs.

2.1 Dataset

We used the Japanese Strategic Research Program for the Promotion of Brain Science (SRPBS) dataset (27) (<https://bcr.atr.jp/decnefpro/data/>), along with additional datasets

obtained from various projects. **Supplementary Table 1** describes the protocols at each site, and **Supplementary Table 2** describes the subject information at each site.

The datasets were collected from the Center of Innovation at Hiroshima University (COI) and the University of Tokyo (UTO), Hiroshima Kajikawa Hospital (HKH), Hiroshima Rehabilitation Center (HRC), Hiroshima University Hospital (HUH), and Yamaguchi University (UYA). COI and UTO follow the unified protocol but HKH, HRC, HUH, and UYA follow non-unified protocols. The total number of HCs and MDD was 543 and 302, respectively, with Beck Depression Inventory-II (BDI-II) scores of 7.5 ± 6.3 and 28.1 ± 10.5 , respectively.

2.2 BOLD signals preprocessing

BOLD signals were preprocessed using fMRIPrep version 1.0.8 (<http://fmripreadthedocs.io/en/1.0.8/workflows.html>) (30). The first 10 s of the data were discarded to allow for T1 equilibration. The preprocessing steps included slice-timing correction, realignment, coregistration, distortion correction using a field map, segmentation of T1-weighted structural images, normalization to Montreal Neurological Institute space, and spatial smoothing with an isotropic Gaussian kernel of 6 mm full width at half maximum. “Fieldmap-less” distortion correction was performed for the test dataset due to the lack of field map data.

2.3 Preprocess of ROI time series for DMD

It is necessary to mitigate the effects of the protocols and physiological noise. BOLD signal extraction was performed using Glasser's 360 regions of interest (ROI) (31), which excluded the cerebellum and contained little white matter.

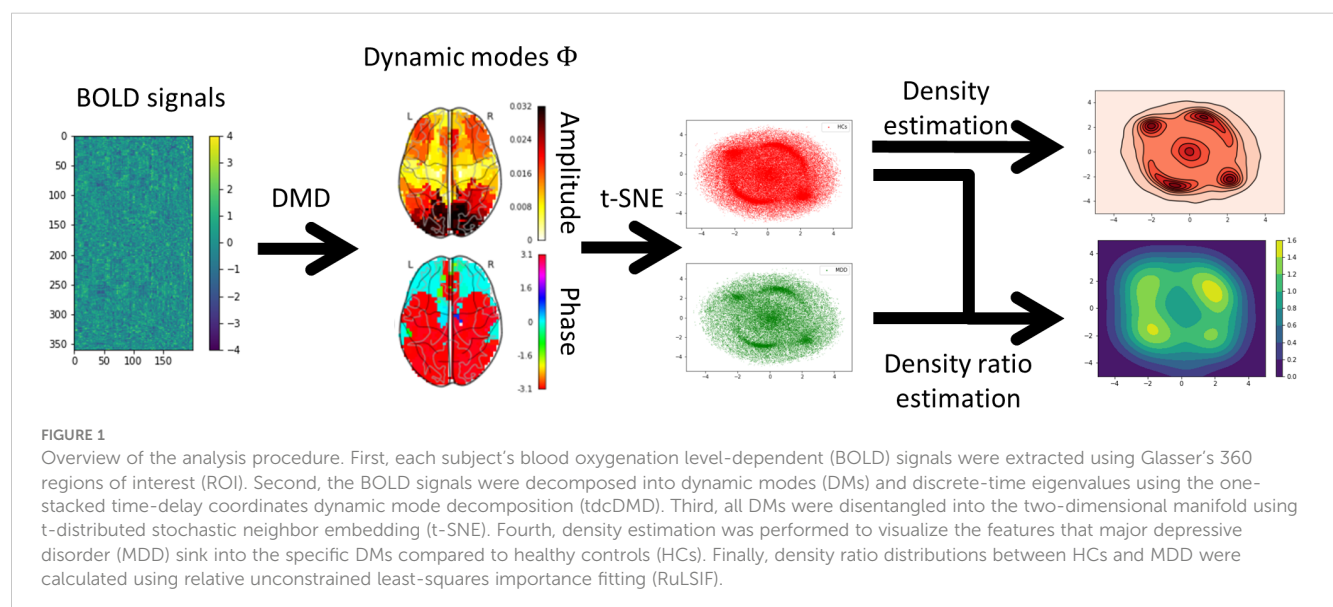


FIGURE 1

Overview of the analysis procedure. First, each subject's blood oxygenation level-dependent (BOLD) signals were extracted using Glasser's 360 regions of interest (ROI). Second, the BOLD signals were decomposed into dynamic modes (DMs) and discrete-time eigenvalues using the one-stacked time-delay coordinates dynamic mode decomposition (tdcDMD). Third, all DMs were disentangled into the two-dimensional manifold using t-distributed stochastic neighbor embedding (t-SNE). Fourth, density estimation was performed to visualize the features that major depressive disorder (MDD) sink into the specific DMs compared to healthy controls (HCs). Finally, density ratio distributions between HCs and MDD were calculated using relative unconstrained least-squares importance fitting (RuLSIF).

Nilearn's NiftiLabelsMasker function (<https://nilearn.github.io/stable/index.html>) was used for the BOLD signal extraction. Detrending was applied to eliminate long-term variations, and BOLD signals were normalized using z-scores to mitigate the effects of the protocols. When analyzed using the DMD, the frequencies were computed for each DM. Therefore, band-pass filtering was not applied.

Confounding factors must be removed when extracting BOLD signals. The fit_transform function was applied to remove confounding factors for the 12 regression parameters (six motion parameters, average signals over the whole brain, and five anatomical CompCor components).

2.4 One-stacked time-delay coordinates DMD

BOLD signals were decomposed into DMs and discrete-time eigenvalues. Time-delay coordinates DMD (tdcDMD) is a method used for decomposing standing waves into spatiotemporal patterns with high accuracy (21); tdcDMD was performed using the dmd.py function in the DMD toolbox (<https://github.com/erichson/DMDpack>). As described in a previous study (26), the BOLD signals of each subject were converted into DMs. As shown in Equation 1, the BOLD signal matrix X was composed of rows representing the number of ROI, N_{roi} and columns representing the number of measurements, N_T .

$$X = [x_1 \ x_2 \ \cdots \ x_{N_T}], \quad (1)$$

where $x_k (\in \mathbb{R}^{N_{roi}})$ represents the BOLD signals at time k . The following matrices were constructed from the BOLD signal matrix X as shown in Equations 2, 3.

$$X_1 = [x_1 \ x_2 \ \cdots \ x_{N_T-1}], \quad (2)$$

$$X_2 = [x_2 \ x_3 \ \cdots \ x_{N_T}], \quad (3)$$

where X_2 represents the matrix with X_1 shifted back one observation. Subsequently, x_{k+1} was stacked on x_k as shown in Equations 4, 5.

$$X_{1aug} = \begin{bmatrix} x_1 & x_2 & \cdots & x_{N_T-2} \\ x_2 & x_3 & \cdots & x_{N_T-1} \end{bmatrix}, \quad (4)$$

$$X_{2aug} = \begin{bmatrix} x_2 & x_3 & \cdots & x_{N_T-1} \\ x_3 & x_4 & \cdots & x_{N_T} \end{bmatrix}, \quad (5)$$

X_{2aug} was predicted using X_{1aug} so $X_{2aug} \approx AX_{1aug}$.

$$A = X_{2aug}X_{1aug}^\dagger, \quad (6)$$

where the dagger represents the generalized inverse. Singular value decomposition was applied to X_{1aug} .

$$X_{1aug} = U\Sigma V^*, \quad (7)$$

where U , Σ , and V represent the left singular, singular value, and right singular matrices of X_{1aug} , respectively. As shown in Equation 8, the matrix A is rewritten by substituting Equation 7 into Equation 6.

$$A = X_{2aug}V\Sigma^{-1}U^*, \quad (8)$$

the proper orthogonal decomposition was applied to A .

$$\tilde{A} = U^*AU = U^*X_{2aug}V\Sigma^{-1}, \quad (9)$$

then eigen decomposition was applied to $\tilde{A}$.

$$\tilde{A}W = W\Lambda, \quad (10)$$

where W and Λ represent the eigenvector and eigenvalue matrices of $\tilde{A}$, respectively. $X_{2aug}V\Sigma^{-1}$ was multiplied from the left in Equation 10 and Equation 9 was substituted into Equation 10.

$$AX_{2aug}V\Sigma^{-1}W = X_{2aug}V\Sigma^{-1}W\Lambda, \quad (11)$$

where $\tilde{A}$ is the similar matrix of A , so they have the same eigenvalue matrix Λ but different eigenvector matrices. In comparing Equations 10, 11, $X_{2aug}V\Sigma^{-1}W$ can be regarded as the eigenvector matrix of A . Finally, the eigen decomposition of A was reconstructed using W and Λ and the dynamic mode matrix Φ was calculated as shown in Equation 12.

$$\Phi = X_{2aug}V\Sigma^{-1}W, \quad (12)$$

the i -th column of Φ , which we denote by $\phi_i (\in \mathbb{C}^{2N_{roi}})$, is the i -th eigenvector of A . The i -th diagonal element of Λ , which we denote by $\lambda_i (\in \mathbb{C})$, is the i -th eigenvalue of A . The phase and amplitude of λ_i mean the frequency and decay rate of the corresponding mode. The frequency f_i corresponding to the dynamic mode ϕ_i and the eigenvalue λ_i is described as following Equation 13.

$$f_i = \frac{\text{imag}(\ln(\lambda_i))}{2\pi\Delta t}, \quad (13)$$

where Δt , $\ln(\cdot)$ and $\text{imag}(\cdot)$ represent the temporal resolution in each protocol, natural logarithm, and the imaginary part of a complex number.

2.5 Two-dimensional manifold with t-SNE

When analyzed using the DMD, pairs of DMs with identical amplitudes but antiphases emerged. Moreover, DMs representing brain states describe intricate curved surfaces in a multidimensional space. In a previous study (26), the modified K-means clustering algorithm was applied to DMs and treated DMs with identical amplitudes and antiphases. However, this approach failed to disentangle intricate curved surfaces in a multidimensional space. Hence, this study employed t-SNE (28) to disentangle the intricate curved surfaces spanned by DMs.

The initial 360 rows, which are inherently independent of the 720 rows of the DMs, were used to employ a one-stacked tdcDMD. Subsequently, the DMs were separated into their real and imaginary components, stacked together, and applied to t-SNE. When t-SNE was applied to all DMs of both HCs and MDD, the perplexity varied from 30 to 10,000. A value of 2,000 was visually selected to achieve maximum separation between peaks within the two-dimensional manifold while keeping `random_state` fixed. The `sklearn.manifold.TSNE` function in Python was employed, with all parameters set to their default values except perplexity and `random_state`.

2.6 Kernel density estimation

It is crucial to select the optimal perplexity at which the peaks within the two-dimensional manifold achieve maximum separation. Hence, we separated the peaks by performing a kernel density estimation on a two-dimensional manifold. The formula for estimating the probability density ρ at a given point y , estimated from points $x_i (i = 1, 2, \dots, n)$ of DMs on the two-dimensional manifold is expressed as following Equation 14:

$$\rho(y) = \sum_i^n K(y - x_i; h), \quad (14)$$

where kernel K is the Gaussian kernel and bandwidth h is set to the Scotts factor. `Scipy.stats.gaussian_kde` function in Python was used (32).

2.7 Kernel density ratio estimation

The probability density was estimated using kernel density estimation on the two-dimensional manifolds obtained by applying t-SNE. Consequently, the distinction between HCs and MDD was revealed as a different balance in the proportion of DMs rather than the emergence of unknown DMs. Hence, we estimated the probability density ratio between HCs and MDD using a relatively unconstrained least-squares importance fitting (RuLSIF) (33). In terms of estimation accuracy, it is more precise to directly estimate the density ratio between HCs and MDD than to indirectly estimate the density ratio by estimating HCs and MDD's densities separately and dividing HCs and MDD's densities. To improve the estimation accuracy, various methods have been developed to directly estimate the density ratio without going through the density estimation process. RuLSIF was chosen for this study because its Python code is publicly available and its calculation speed is fast.

The optimal parameters were automatically selected in the range of coefficient $\alpha = 0$, the regularization parameter $\eta = 0.10, 0.09, \dots, 0.01$, and Gaussian kernel width $\sigma = 1.2, 1.0, 0.8$. RuLSIF was performed using the toolbox (https://github.com/hoxo-m/densratio_py).

To estimate the density ratio of the area where the HCs' density was higher than the MDD's density, the HCs' manifold was used as the denominator, and the MDD's manifold was used as the

numerator. To estimate the density ratio for the area where the MDD's density was higher than the HCs' density, the MDD's manifold was used as the denominator, and the HCs' manifold was used as the numerator.

2.8 Plotting dynamic modes, histogram of frequency, and discrete-time eigenvalues greater than 95% significance level

Kernel density ratio estimation was used to calculate the probability density ratio between HCs and MDD. However, the specific regions exhibiting significant differences in terms of density ratio between HCs and MDD remain unknown. To solve this problem, permutation tests were performed to clarify areas higher than the 95% significance level and to plot the mean amplitude and phase of the DMs, a histogram of frequency, and discrete-time eigenvalues within the significant areas.

First, we randomized the labels of the HCs and MDD in a two-dimensional manifold. Second, with fixed parameters $(\alpha, \sigma, \eta) = (0, 1.0, 0.01)$, RuLSIF was performed to calculate the maximum peak value, repeating this process 100 times. Third, we applied the density-based spatial clustering of applications with noise (DBSCAN) (34) to cluster points within areas that exhibited maximum peak values higher than the 95th percentile. Finally, we plotted the mean amplitudes and phases of the DMs, frequency histograms, and discrete-time eigenvalues λ associated with each cluster. For the density ratios $p_{\text{MDD}}(x)/p_{\text{HCs}}(x)$ and $p_{\text{HCs}}(x)/p_{\text{MDD}}(x)$, the DBSCAN parameters were set as $(\text{eps}, \text{min samples}) = (1, 100)$ and $(0.15, 300)$, respectively. Points that were not assigned to a cluster were excluded.

3 Results

3.1 Applying t-SNE, density estimation, and density ratio estimation to the DMs

First, the two-dimensional manifold was calculated by applying t-SNE to all DMs across all subjects and was visualized after separating the HCs and MDD (Figure 2A: HCs, B: MDD). Second, the perplexity was varied from 30 to 10,000 and consequently set to 2,000 to maximally separate the peaks in the two-dimensional manifold. Finally, kernel density estimation was performed to clarify the distribution features exhibited by the two-dimensional manifold (Figure 2C: HCs, D: MDD).

In the HCs, the peaks displayed a relatively uniform distribution (Figure 2C). Conversely, in the MDD group, the peaks exhibited a bias toward the upper right, lower left, and central areas (Figure 2D). In other words, MDD tended to sink more into specific DMs than HCs. In addition, the edge of the MDD manifold appeared slightly wider than that of the HCs manifold at the elliptical periphery. To assess these features, density ratio estimation was performed by applying RuLSIF to the two-dimensional manifolds.

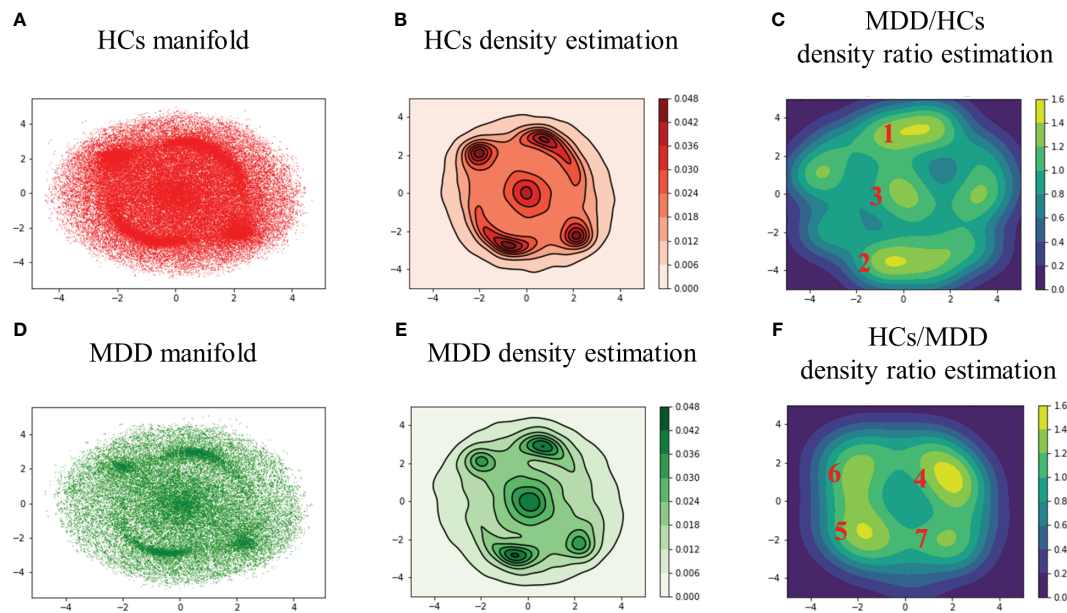


FIGURE 2

Two-dimensional manifolds of HCs (A) and MDD (B) with t-SNE, kernel density estimation of HCs (C) and MDD (D), and density ratio distribution estimated by relative unconstrained least-squares importance fitting (RuLSIF) in the case of MDD/HCs (E) and HCs/MDD (F). The points on the two-dimensional manifold indicate DMs (A, B). The curved lines on the density estimation indicate contour lines (C, D). The red numbers indicate the peak number. In the MDD/HCs case, the peaks located at the far left and far right were not assigned numbers due to their lack of significance at the 95% confidence level (E, F). MDD/HCs shows increased DMs in MDD, and HCs/MDD shows reduced DMs in MDD.

3.2 DM's features in the clusters

The density ratio was calculated using HCs as the denominator and MDD as the numerator (Figure 2E). Similarly, the density ratio was calculated using the MDD as the denominator and HCs as the numerator (Figure 2F). The colored bars represent the value of the density ratios. For parameter search, $\alpha = 0$, the regularization parameter η varied from 0.10 to 0.01, and the Gaussian kernel width σ took values of 1.2, 1.0, and 0.8. As a result, $\eta = 0.01$ and $\sigma = 1.0$ were selected. After performing the density ratio estimation, it was necessary to determine the significant areas. Therefore, a permutation test was performed with $\alpha = 0$, $\eta = 0.01$, and $\sigma = 1.0$. The labels of HCs and MDD across all DMs were shuffled, and density ratio estimation was applied to calculate the maximum peak value 100 times (Supplementary Figure S1). Subsequently, areas above the 95th percentile of the maximum peak value were calculated (Supplementary Figures S2A, B) and clustered using DBSCAN (Supplementary Figures S2C, D).

Glass brain plots depicting the amplitude and phase of the mean DMs, histograms of frequency, and discrete-time eigenvalues within clusters in the MDD/HCs (Figure 3) and HCs/MDD (Figure 4) cases are presented. Because DMs appear in pairs with modes of identical amplitude and an anti-phase relationship, DMs at symmetric locations are paired (Figure 2E 1-2, Figure 2F 4-5, and 6-7).

In the MDD/HCs case, the glass brain plots of DM1 and DM2 were similar to those of DMN. The discrete-time eigenvalues were distributed along the unit circle, indicating stability in DM1 and

DM2. The glass brain plots of DM3 were similar to those of the SMN. The discrete-time eigenvalues were relatively numerous inside the unit circle, indicating not only stability but also convergence in DM3. Additionally, because both the DMN and SMN were concurrently active in DM2, the frequency histogram was likely to show an intermediate distribution between the distributions in DM1 and DM3.

In the HCs/MDD case, the glass brain plots of DM4 and DM5 were similar to those of the VN. The discrete-time eigenvalues were distributed along the unit circle, indicating stability in DM4 and DM5. The histogram of the frequency showed a peak at approximately 0.03 Hz. The glass-brain plots of DM6 and DM7 were similar to those of the SN. The discrete-time eigenvalues were distributed along the unit circle, indicating stability in DM6 and DM7. The histogram of the frequency showed a peak at approximately 0.15 Hz. The small number of DMs in DM7 likely resulted in a negative bias of the phase and scattering of the frequency histogram.

4 Discussion

We devised a methodology for estimating brain-state stability across subjects by applying DMD to BOLD signals; t-SNE was applied to the DMs to disentangle the intricate curved surface spanned by the DMs into a two-dimensional manifold (Figure 2). Density ratio estimation was then performed on the two-dimensional manifolds of HCs and MDD (Figures 2E, F).

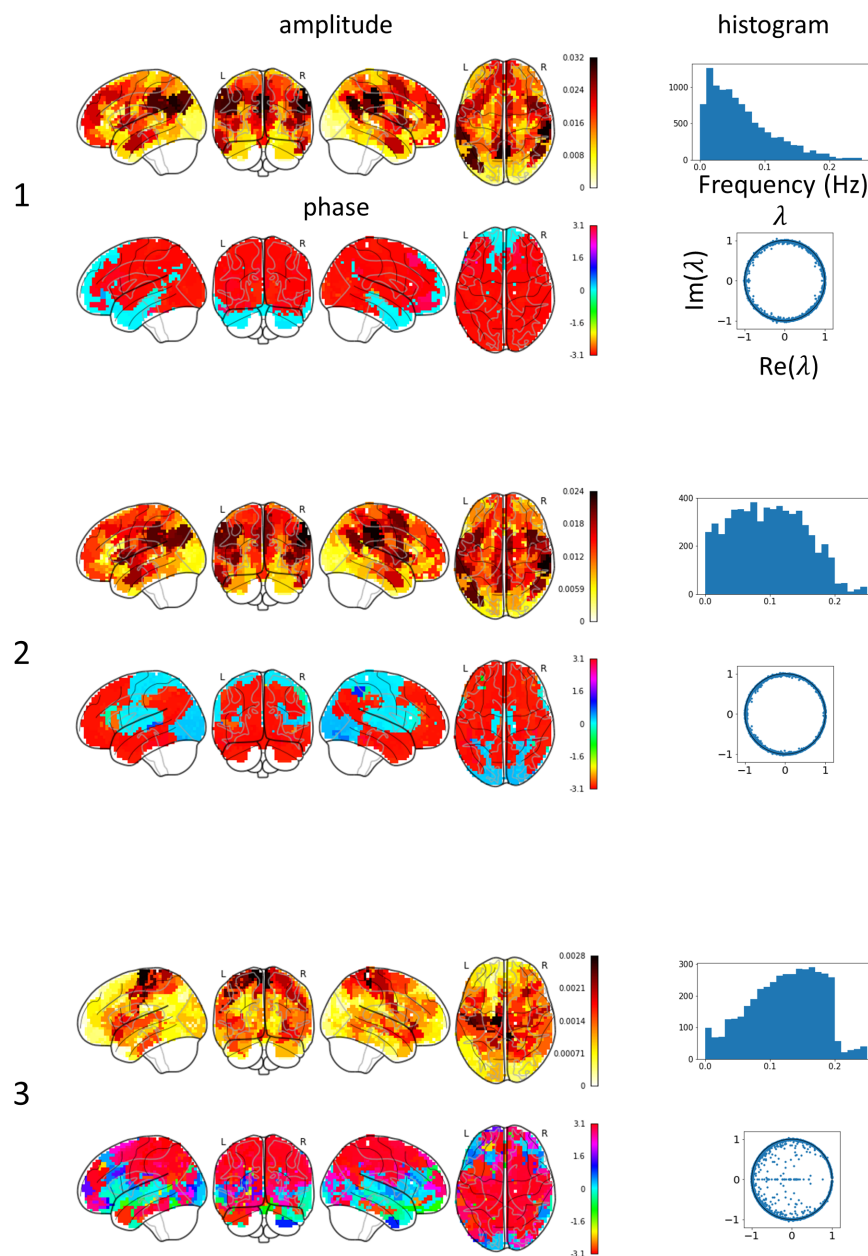
MDD/HCs glass brain plot of DMs, histogram of frequency, and λ 

FIGURE 3

Mean DMs' amplitude, phase, histogram of frequency, discrete-time eigenvalue λ in each MDD/HCs cluster. The left numbers correspond to the peak numbers in Figure 2. DM1 resembles the default mode network (DMN), has a low frequency, and is stable. DM2 resembles DMN, has a flat frequency, and is stable. DM3 resembles a sensory-motor network (SMN), has high frequency, and tends to converge.

Consequently, it was revealed that MDD did not cause the emergence of unknown DMs distinct from HCs but sank into specific DMs, such as DM1, DM2, and DM3.

In machine learning using DMD, there are two important aspects of comparing HCs and MDD. One is interpretability in terms of physiology and the other is classification performance for biomarker. Therefore, individual-level classification between HCs and MDD was performed to demonstrate usability to the biomarker development (Supplementary Figure S6). As a result, when evaluated using 10-fold cross-validation (Supplementary Figure S7), the balanced accuracy

(Bacc) was slightly better than that in the previous study (12) using sFC (Supplementary Figure S8).

4.1 Dynamic modes and cortical abnormalities of MDD

The spatial patterns of reduced DMs corresponded to the patterns observed in the cortical thickness and surface area abnormalities (29). Specifically, DM6 and DM7 exhibited spatial

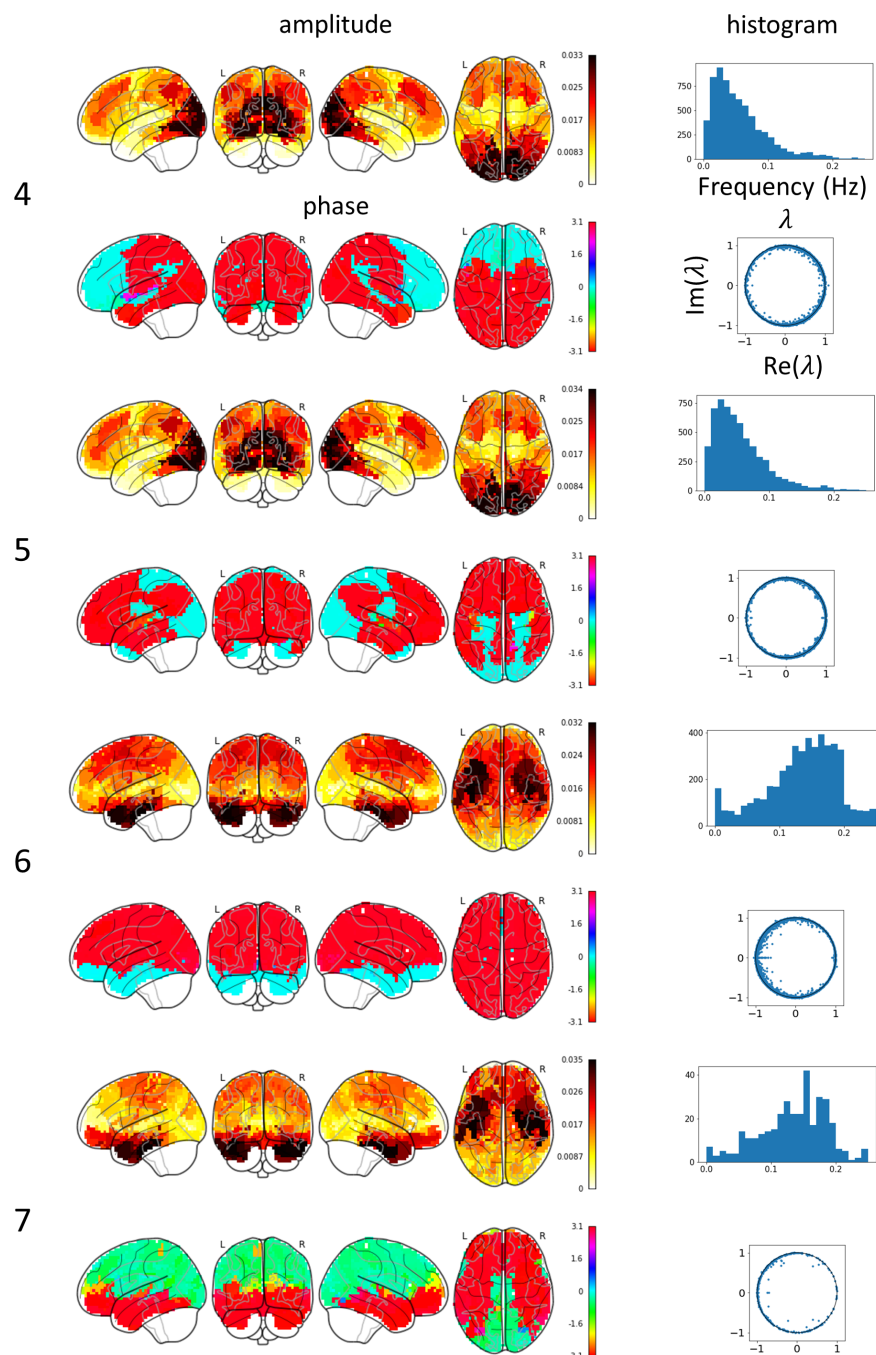
HCs/MDD glass brain plot of DMs, histogram of frequency, and λ 

FIGURE 4

Mean DM's amplitude, phase, histogram of frequency, discrete-time eigenvalue λ in each HCs/MDD cluster. The left numbers correspond to the peak numbers in Figure 2. DM4 resembles a visual network (VN), has a low frequency, and is stable. DM 5 resembles a VN, has a low frequency, and is stable. DM6 resembles a salience network (SN), has a high frequency, and is stable. DM 7 resembles an SN, has a high frequency, and is stable.

patterns similar to the reductions in cortical thickness observed in adult MDD, whereas DM4 and DM5 displayed spatial patterns resembling the reductions in cortical surface area observed in adolescent MDD. Therefore, the reduction in DM4, DM5, DM6, and DM7 levels plays a key role in elucidating the mechanisms of MDD.

Widespread abnormalities have been discovered in MDD, from microscopic phenomena such as the genome and molecular pathways to macroscopic phenomena such as BOLD signals. Microscopic mutations are environmentally influenced, promote synaptic degeneration with inflammation, lead to mesoscopic neuronal firing abnormalities weighted by the neurotransmitter

map, and result in macroscopic abnormalities, such as BOLD signals (35–39). Related to mesoscopic phenomena, some abnormalities are observed in the reuptake of neurotransmitters, such as serotonin, dopamine, norepinephrine, and GABA (40–42) resulting in neurotransmitter concentrations in plasma metabolism (43). Related to macroscopic phenomena, MDD exhibits reduced cortical thickness and surface area compared with HCs (29). As if to connect these two different scale phenomena, both the cortical abnormalities and receptor maps share similar spatial patterns (44, 45). These combined abnormalities likely resulted in sinking into specific DMs, such as DM1, DM2, and DM3. Hence, if a subject transitions from HCs to MDD, it is plausible that MDD would submerge into these particular DMs alongside reductions in cortical thickness and surface area, as well as neurotransmitter reuptake abnormalities.

As a first step in integrating multiple pieces of information that reflect different aspects of MDD, it is vital to investigate the relationship between alterations in stability based on DMs and reductions in cortical thickness and surface area using large datasets. In a comprehensive study on white matter alterations in HCs and MDD, fractional anisotropy was found to be decreased in adult MDD but not significantly different in adolescent MDD compared to HCs (46). Conversely, adolescent MDD exhibited decreased cortical surface areas, particularly in regions such as the orbitofrontal cortex and lateral occipital cortex, when compared to HCs (29). Therefore, in addition to examining the structural connectivity based on the fiber structure in the white matter, it is essential to consider stability measures based on reduced cortical surface areas in both HCs and MDD. Notably, sFC can be well explained (approximately 0.9) by geometric modes (GMs) derived from the cortical geometric structure in HCs (47), suggesting that GMs could serve as a valuable stability indicator based on brain structure.

The integration of multiple indicators will be effective in psychiatric care. A combination of temporally stable trait biomarkers and temporally variable state biomarkers is necessary for early diagnosis and intervention using mechanism-based treatments (48). Therefore, structural connectivity and GMs, as temporally stable trait biomarkers, are employed as criteria for assessing stability. Additionally, DMs serve as temporally variable state biomarkers for evaluating the current cortical stability. The integration of the stability associated with cortical structural and geometric alterations and BOLD signals may shed light on previously unknown mechanisms underlying MDD.

4.2 Inconsistency with the previous studies

In MDD, negative emotions are associated with increased activity in the DMN (49) and motor impairment is associated with slow gait and slumped posture (50). Consequently, DM1 and DM2, resembling the DMN, probably emerged for experiencing negative emotions, and DM3, resembling the SMN, probably emerged for experiencing movement difficulties.

In the EL-based method (20), non-melancholic MDD tended to sink into the left CEN, whereas melancholic MDD tended to sink

into both the left CEN and dorsal DMN states. In contrast, in the DMD-based method, the MDD sinks into brain states resembling the DMN and SMN. These differences can be attributed to the following three factors. First, the binarization process affects the results. In the DMD-based method, the strong amplitudes of all DMs, except for DM3, were approximately 0.03 in regions associated with the DMN, VN, and SN, and medium amplitudes were approximately 0.01 in regions associated with the SMN. In contrast, the strongest amplitudes of DM3 were associated with the SMN, but the amplitude value was only 0.003, which is approximately 1/10 compared with the other DMs. Conversely, the EL-based method requires the binarization of BOLD signals after functional network assignment to a specific region. This binarization process may have led to an outcome in which regions with amplitudes smaller than the average were considered inactive. Second, the larger number of subjects in our study may lead to more robust results than the previous study. This study included 845 subjects, whereas the previous study included 262 subjects. Lastly, regarding the subtype of MDD, this study did not differentiate between non-melancholic and melancholic MDD, whereas previous studies analyzed these subtypes separately. These methodological discrepancies and different numbers of subjects may account for the sinking into different states between the DMD- and EL-based methods.

In a large dataset study using the sFC (13), hypoconnectivities were observed within the SMN and SN, as well as between the SMN, SN, dorsal attention network (DAN), and VN in MDD. However, no significant differences were found between the DMN and fronto-parietal networks (FPN). In contrast, this study identified abnormalities in the DMN, SMN, VN, and SN but no abnormalities in the DAN. A previous study using the same dataset showed that there were only a few abnormal FCs related to the DAN and many abnormal FCs related to the DMN (12). It is worth noting that the DMN and DAN exhibit an inverse correlation, wherein DAN activation leads to DMN suppression (51). Therefore, it is possible that the subjects in this study activated the DMN, while those in the larger dataset study used an sFC-activated DAN (13).

4.3 Relationships among DMs' spatial pattern, histogram of frequency, and discrete-time eigenvalue

The amplitude of DM3 exhibited a spatial pattern resembling that of the SMN and was approximately 0.003, which was approximately 1/10 smaller than the amplitudes of the other DMs. The amplitudes in DM6 and DM7 were stronger in the SN and slightly stronger in the SMN than in the other DMs. The amplitudes of DM1 and DM2 were stronger in the DMN and slightly stronger in the SMN. Consequently, the SMN tended to appear more frequently in conjunction with other networks. Furthermore, the observation that the SMN tended to co-occur with low-frequency DM1 and DM2, as well as high-frequency DM6 and DM7, suggests that DM3 transmitted information across a broad range of frequencies, resulting in a smoother frequency distribution compared to the other DMs.

A comparative study investigating empirical and simulated sFC and dFC proposed that SMN serves as a driver of cortical dynamics (52). The SMN probably exhibits weak amplitudes and a wide frequency range across all DMs because of its role as a driver in cortical dynamics.

4.4 Limitation of the current method

t-SNE was employed to disentangle the intricate curved surfaces spanned by the DMs and analyze the inter-subject stability. However, the method used in the study encountered two problems. First, the computation time was considerable, requiring approximately one week to apply t-SNE to approximately 160,000 DMs, search for the optimal perplexity, estimate the density ratio using RuLSIF, and calculate the clusters based on permutation tests. Consequently, the search for optimal parameters was limited to perplexity during the t-SNE. It is noteworthy that t-SNE encompasses additional parameters, including the early exaggeration factor, learning rate, angle, and random_state, which also influence the manifold. These parameters were determined using a heuristic method (53) in the sklearn.manifold. Second, memory usage has become a serious concern as increasing the perplexity of t-SNE consumes up to approximately 100 GB. To analyze larger datasets, alternative methods such as deep learning or other approaches need to be developed.

When performing rsfMRI, some subjects rarely lacked BOLD signals in the cerebellum. Additionally, BOLD signals from the white matter often contain significant noise. To avoid these issues, the stability analysis between HCs and MDD in this study utilized Glasser's 360 ROI, which excludes the cerebellum and predominantly consists of gray matter. Therefore, to analyze intersubject stability using ROI that includes the cerebellum and white matter, alternative methods such as deep learning or other approaches need to be developed instead of this method.

Supplementary Figure S5 shows the normalized number of DMs for each protocol, which was obtained by dividing the number of DMs in the cluster by the total number of DMs in the protocol. The COI and UTO employed a unified protocol, whereas HKH, HUH, HRC, and UYA employed independent protocols. However, the normalized histogram of site in COI tended to be closer to UYA and HKH, while the normalized histogram of site in UTO tended to be closer to HUH and HRC. Supplementary Table 1 showed that Siemens manufactured COI, UYA, and HKH while GE manufactured UTO, HUH, and HRC. The inter-protocol differences in DM6 and DM7 were more dependent on manufacturers such as Siemens and GE than on protocol unification (Supplementary Table 1). In a previous study on physiological noise (54), the approximately 0.2 Hz component of BOLD signals was affected by respiration. In addition, the FD values of DM 6 and 7 were higher than those of other DMs, as shown in Supplementary Figures S3, S4. However, the Bacc in the case of using all frequencies was higher than that of using 0.01–0.08 Hz, as

shown in Supplementary Figure S8. Thus, as in previous research (26), there are more spontaneous fluctuations representing cortical dynamics than noise associated with respiration, head movement, and manufacture.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The SRPBS dataset except for UYA can be downloadable from the DecNef Project Brain Data Repository. UYA is available to only our research group. Requests to access these datasets should be directed to <https://hbm.brainminds-beyond.jp/data.html>.

Ethics statement

The studies involving humans were approved by Yamaguchi University [H23-153 and H25-85]. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HE: Conceptualization, Formal analysis, Writing – original draft, Investigation, Methodology, Software, Visualization. SI: Conceptualization, Investigation, Methodology, Software, Writing – review & editing. KH: Data curation, Writing – review & editing. HY: Data curation, Writing – review & editing. TM: Data curation, Writing – review & editing. KM: Data curation, Writing – review & editing. YK: Methodology, Writing – review & editing. OY: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2024.1288808/full#supplementary-material>

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Fronto-striato network function is reduced in major depressive disorder

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Introduction: Major depressive disorder (MDD) is a major cause of poor quality of life and disability and is highly prevalent worldwide. Various pathological mechanisms are implicated in MDD, including the reward system. The human brain is equipped with a reward system that is involved in aspects such as motivation, pleasure, and learning. Several studies including a meta-analysis have been reported on the reward system network and MDD. However, to our knowledge, no studies have examined the relationship between the reward system network of drug-naïve, first-episode MDD patients and the detailed symptoms of MDD or age. The fronto-striato network (FSN) is closely related to the reward system network. The present study primarily aimed to elucidate this point.

Methods: A total of 89 drug-naïve first-episode MDD patients and 82 healthy controls (HCs) patients were enrolled in the study. The correlation between the FSN and age and the interaction between age and illness in the FSN were investigated in 75 patients in the MDD group and 79 patients in the HC group with available information on the FSN and age. In addition, the association between the FSN and the total scores on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) and scores in each symptom item was analyzed in 76 MDD subjects with information on the FSN and HAM-D-17. The significance of each result was evaluated according to a p-value of <0.05.

Results: Age was inversely correlated with the FSN ($p=2.14e-11$) in the HC group but not in the MDD group ($p=0.79$). FSN varied with the presence of MDD and with age, particularly showing an interaction with MDD and age ($p=1.04e-08$). Specifically, age and the presence or absence of MDD each affected FSN, but the effect of age on FSN changed in the presence of depression. FSN did not correlate with total HAM-D-17 scores or scores in each item.

Discussion: The reward system may be dysfunctional in patients with MDD. In addition, the effect could be greater in younger patients. Meanwhile, there is no correlation between the function of the reward system and the severity of MDD or the severity of each symptom. Thus, the reward system network may be an important biological marker of MDD, although careful consideration should be given to age and its association with the severity of the disorder.

Conclusion: The reward system function is decreased in MDD patients, and this decrease may be more pronounced in younger patients, although further research is still needed.

KEYWORDS

major depression, reward system, striatum, prefrontal cortex, first episode

1 Introduction

Major depressive disorder (MDD), which presents with symptoms including depressed mood, decreased interest in activities, and reduced experience of pleasure, is a leading cause of reduced quality of life and disability. According to the World Health Organization, depression affects more than 300 million people worldwide, accounting for approximately 4.4% of the population (1). It is multifaceted and involves a combination of genetic, environmental, and neurobiological factors. For example, altered neurotransmission and abnormalities in the hypothalamus–pituitary–adrenal axis related to chronic stress, inflammation, reduced neural plasticity, and network dysfunction have been reported (2).

Humans and many other animals have a neural circuit called the reward system that is activated when a need is satisfied or is expected to be satisfied and produces a pleasant sensation in the individual. The reward system is involved in key components of behavior such as motivation, pleasure, and learning (3). The reward system uses dopamine as its primary neurotransmitter (4), and it consists of a network involving the ventral tegmental area of the midbrain, nucleus accumbens and posterior striatum of the basal ganglia, amygdala, and cingulate cortex of the limbic system, and frontal association areas among other areas of the frontal lobe (5, 6). The basal ganglia are involved in reward responses, behavioral choices, learning, and memory (7), while the frontal lobes are involved in reward-based decision-making, cognitive control, and emotion regulation (8).

The pathophysiology of MDD is unlikely to result from a single brain region or neurotransmitter system, and MDD is now conceptualized as a multidimensional system-level disorder affecting discrete but functionally integrated pathways (9). One important factor of this has been suggested to be a possible abnormality in the neural circuitry of MDD. Particularly, a link between MDD and the reward system has been noted. Neuroimaging studies have pointed to dysfunctions in the prefrontal cortex and striatum, which regulate the limbic system and brainstem structures involved in mediating emotional behavior, during the development of MDD (10). In addition, patients with MDD have reduced strength of

functional connections between the ventral striatum and the ventral medial prefrontal and anterior cingulate cortices (11), which may be related to abnormalities in reward processing, motivation, and anhedonia. There are five cortico-basal ganglia loop circuits, namely, the motor loop, oculomotor loop, dorsolateral prefrontal loop, lateral orbitofrontal loop, and anterior cingulate gyrus loop circuits (12, 13). A recent meta-analysis demonstrated dysfunctions of reward processing behavior in MDD, demonstrating that depression was associated with small to moderate reward-processing impairments and of varying magnitudes across several reward-processing subdomains (14). This is important because the cognitive and neural mechanisms underlying reward processing and its subdomains are relatively well understood (14). Therefore, the reward system function may be a biological marker for MDD, and interventions that improve the reward system function may be effective in treating MDD. Further, the reward system may be a new therapeutic target. We previously used structural imaging to investigate the structural covariance network in the brain and extracted the fronto-striato network (FSN) (15). This network consists of the striatum and prefrontal cortex and is closely associated with the reward system (16).

Although an association between MDD and the reward system based on the fronto-striato-parietal network has been suggested, to our best knowledge, no study has investigated the effects of first-onset, drug-naïve MDD and age on the fronto-striato-parietal network. Recent evidence supports that the effect of age goes beyond the prefrontal cortex and includes adaptive connectivity changes in the fronto-striato-parietal network (17). Thus, age may influence the FSN. Therefore, this study aimed to investigate the influence of MDD and age on FSN, as well as the association between FSN and the severity of MDD and each symptom, using the structural connectivity method in first-episode, medication-naïve MDD patients and healthy subjects.

2 Materials and methods

2.1 Participants

MDD patients were recruited from the university hospital of the University of Occupational and Environmental Health, Japan. Consecutive patients presenting at the Occupational and Medical

Abbreviations: fMRI, functional magnetic resonance imaging; FSN, fronto-striato network; HAM-D-17, 17-item Hamilton Rating Scale for Depression; HCs, healthy controls; ICA, Independent Component Analysis; MDD, major depressive disorder.

University Hospital with a first episode of MDD and no medication use were recruited. MDD was diagnosed through a fully structured clinical interview using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision Research Edition, and the Structured Clinical Interview for DSM Disorders Non-Patient Version. The inclusion criterion was never meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria for Axis I disorders during a psychiatrist interview. The exclusion criteria were as follows (1): mild cognitive impairment as assessed using the Mini-Mental State Examination (2); Mini-Mental State Examination scores of <27 (3); history of neurological disease or the presence of Axis I (e.g., schizophrenia, other affective disorders) or Axis II (e.g., personality disorders, mental retardation) psychiatric disorders (4); comorbid substance use disorders; and (5) unwillingness to provide informed consent. Depression severity was assessed using the 17-item Hamilton Rating Scale for Depression (HAM-D-17) (18). None of the MDD patients in the study had a previous episode of mood disorder. Healthy controls (HCs) were recruited from the neighborhood; the HC group had never been diagnosed with a mental illness based on the findings of the SCID.

This study was approved by the Ethical Review Board of our institution and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to their participation in this study.

2.2 MRI acquisition

Magnetic resonance imaging was performed using a 3T MR system (Signa EXCITE 3T; GE Healthcare, Waukesha, WI, USA) equipped with an eight-channel brain phased-array coil. Rather than assessing functional connectivity at rest, this study utilized a structural covariance network based on brain structural imaging. The original T1 images were acquired using three-dimensional (3D) fast-spoiled gradient-recalled acquisition in a steady state. The acquisition parameters were set as follows: repetition time, 10 ms; echo time, 4.1 ms; inversion time, 700 ms; flip angle, 10°; field-of-view, 24 cm; section thickness, 1.2 mm; and resolution, $0.9 \times 0.9 \times 1.2$ mm. All images underwent correction for image distortion due to gradient non-

linearity using the Grad Warp software program (19) and for intensity inhomogeneity with the “N3” function (20).

2.3 Network extraction

In this study, 3D T1-weighted images were used to analyze the structural covariance network. we initially employed a data-driven approach using the network extraction method described in our previous study. This method leverages Source-based Morphometry and Independent Component Analysis (ICA) to identify naturally occurring covariance patterns across brain regions. First, gray matter segmentation, normalization, and modulation were analyzed using Statistical Parametric Mapping 12 (Institute of Neurology, London, UK) software, employing a fully automated method as described by Ashburner (21, 22). The resulting modulated gray matter images were smoothed using an 8-mm full-width-at-half-maximum Gaussian kernel. Subsequently, the GIFT toolbox (<https://icatb.sourceforge.io/groupica.htm>) with minimum length was employed to estimate the independent components from all modulated gray matter images of HCs and patients with MDD. ICA was performed using a neural network algorithm (Infomax), and reliability was ensured by repeating the ICA 20 times using the ICASSO algorithm (<https://research.ics.aalto.fi/ica/icasso/>). The source matrix was used to determine the association between IC and voxels, whereas the mixing matrix included a loading coefficient to illustrate the relationship between each subject and each component. Sixteen networks were extracted based on the required minimum description length. The source matrix was then converted back into a 3D image to visualize structural networks, scaled to unit standard deviations (Z maps), and defined as $|Z| > 2.5$. A neuroradiologist reached a consensus to delineate the network representing the FSN (Figure 1). To improve the quality of the network images, a detailed list of coordinates and regions for each network was added (Table 1). This clarified the specific brain regions and their coordinates for each network, including the FSN, and ensured that the reward network was accurately represented. This also clarified the distinction between ventral-frontal-striatal and dorsal-frontal-striatal areas.

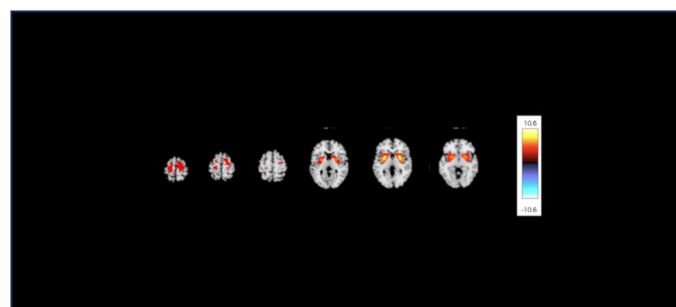


FIGURE 1

The structural covariance network of the fronto-striato network with $|Z| > 2.5$. The red/yellow colors correspond to regions in which the voxel volumes show a positive correlation.

TABLE 1 Structural covariance networks.

Anatomical regions	Volume (cc) left/right	Max z-value for left/right hemisphere (Talairach coordinates x, y, z)
Transverse temporal gyrus	1.0/1.0	11.9 (-42, -30, 13)/5.1 (46, -23, 11)
Superior temporal gyrus	11.5/6.7	11.5 (-43, -31, 17)/6.5 (53, -10, 3)
Insula	3.8/3.6	10.6 (-46, -31, 20)/6.1 (45, -27, 19)
Inferior parietal lobule	4.5/2.6	8.4 (-52, -35, 24)/6.2 (52, -29, 24)
Postcentral gyrus	1.7/2.6	8.3 (-52, -27, 18)/5.5 (55, -28, 21)
Sub-gyral	1.8/0.6	6.7 (-40, -34, 22)/4.9 (42, -27, 22)
Precentral gyrus	0.8/3.0	4.7 (-46, -13, 8)/4.9 (55, -7, 6)
Middle temporal gyrus	2.1/0.4	4.4 (-56, -5, -5)/4.6 (58, -2, -4)

2.4 Statistical analysis

Pearson’s correlation coefficient was used to examine the correlation between the FSN and age in the MDD and HC groups. In addition, in each group, FSN was used as the dependent variable and age and sex as independent variables, and multiple regression analysis was performed to check the p-value, thereby adjusting for the effect of sex in the two groups. We also analyzed the interaction of age and disease status in relation to FSN after adjusting for sex. Spearman’s correlation coefficient was used to examine the correlation between the FSN and each HAMD-17 item. To eliminate the problem of multiple comparisons, the results were processed using the Benjamini–Hochberg method. All statistical analyses were performed using EZR software version 4.0.2 (Developer: Kanda, Y.; Address: Saitama Medical Center, Jichi Medical University, Saitama, Japan), with p-values less than 0.05 considered statistically significant.

3 Results

A total of 89 patients with drug-naïve first-episode MDD and 82 HCs were enrolled. Overall, 75 patients in the MDD group and 79 individuals in the HC group for whom information on age and FSN was available were included in the analysis of the correlation between FSN and age and the interaction between age and disease on FSN. To analyze the association between the FSN and HAMD-17, 76 patients in the MDD group with information on the FSN and HAMD-17 were included. The primary background factors are listed in Table 2.

3.1 Effects of depression and age on FSN

Figure 2 shows the results of the correlation analysis between age and FSN in the HC and MDD groups. Age was significantly

TABLE 2 Background characteristics of patients with MDD and healthy controls.

	MDD patients (n=89)	Healthy controls (n=82)	p Value
Age (years)	54.78 ± 16.23 (n=86)	35.40 ± 12.05 (n=82)	<0.01*
Males/females	39/47	56/26	0.03*
FSN	-0.24 ± 0.93 (n=77)	0.23 ± 1.02 (n=79)	0.03*
Total HAMD-17 score (0–52)	21.71 ± 7.32 (n=83)	–	

*Statistically significant (p<0.05).
MDD, major depressive disorder; FSN, fronto-striato network; HAMD-17, 17-item Hamilton Rating Scale for Depression.

correlated with FSN in the HC group but not in the MDD group. Age had a significant effect on FSN in the HC group even after adjustment for sex, while age had no significant effect on FSN in the MDD group even after such adjustment (Table 3). The effects of age and the presence of disease on FSN are shown in Table 4. There was a significant interaction between age and presence of disease.

3.2 Correlation of FSN with total HAMD-17 score and each HAMD-17 item score

There was no correlation between FSN and the total HAMD-17 scores or each item score (Table 5).

4 Discussion

This study compared the relationship of FSN with age between healthy subjects and patients with depression and analyzed the effects of the presence of MDD, age, and their interactions on FSN. The results showed an inverse relationship between FSN and age in HCs, whereas this relationship did not exist in patients with MDD. Furthermore, the FSN was significantly affected by both the presence of disease and age, indicating a significant interaction between the two.

The inverse relationship between FSN and age in HCs suggests that the function of this network diminishes with age. A previous study, in which network extraction was performed by functional magnetic resonance imaging (fMRI), also found a negative association between age and brain network connectivity, including the default mode network that contains the superior and middle frontal gyri, posterior cingulate, middle temporal gyrus, and superior parietal region (23). Meanwhile, the FSN is involved in reward processing, motivation, and decision-making in patients with MDD. However, this inverse correlation was not found in patients with MDD in the current study. This indicates that the younger the patient with MDD, the lower the FSN function and the lower the age-related correlation. Considering the inverse correlation found in HCs, these results suggest that in MDD, the FSN function is lower in younger patients and this phenomenon is

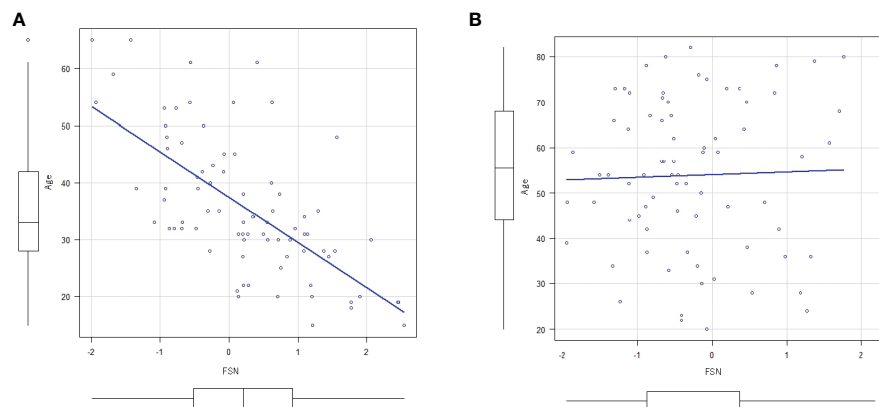


FIGURE 2

Correlation between FSN and age. **(A)** There is an inverse correlation between FSN and age (correlation coefficient=0.666, $p<0.01$) in the HC group. **(B)** There is no inverse correlation between FSN and age ($p=0.79$) in the MDD group (bottom row). FSN, fronto-striato network; HC, healthy controls; MDD, major depressive disorders.

no longer present as aging progresses. This indicates that MDD has a neurobiological basis and that abnormalities in the FSN, which are assumed to be related to the reward system, contribute to depressive symptoms. Further, FSN dysfunction may be a biological marker for the diagnosis for MDD. A large amount of evidence indicates a link between MDD and the reward system. Blood flow differences have been observed in regions associated with the dopaminergic system (24), and the levels of homovanillic acid, a dopamine metabolite, are decreased in the cerebrospinal fluid and transvenous plasma of patients with MDD (25, 26). The noted changes in central dopaminergic function in MDD provide indirect evidence of dysfunction of the reward system in MDD.

fMRI studies have demonstrated that dopaminergic neurons project from the ventral tegmental area of the midbrain to several brain regions, including the nucleus accumbens (25, 26). One fMRI study showed that MDD patients on long-term medication have reduced responses to reward learning signals, particularly in the ventral striatum and anterior cingulate gyrus (27). Functional neuroimaging studies of patients with MDD have shown that ventral striatal regions, such as the nucleus accumbens, are less active, and orbitofrontal cortex activity is elevated during reward tasks (28). The reward system is a network of multiple regions, and reports indicate that all regions comprising the reward system are altered in patients with MDD, providing indirect evidence for reward system dysfunction in MDD. The reward system is considered a network in the brain, and some studies have indicated to a link between MDD and the reward system network. A resting-state fMRI study focused on the nucleus accumbens-based reward system circuitry in patients with MDD confirmed the important role of reduced functional coupling in the reward network in the neuropathology of MDD (29). Our report focused on how age affected the association between MDD and the reward network, and the findings may help in further understanding the relationship between MDD and reward system dysfunction. The interaction between age and the presence of disease shown in this study indicated that MDD may have a specific effect on age-dependent changes in the FSN. This

underscores the importance of considering age in the treatment and management of MDD and suggests the possible need for an individualized approach for patients with depression in different age groups.

The current study also found that the FSN was not correlated with the total HAMD-17 score or each item score in MDD patients. The ability to predict when and where rewards will occur plays an important role in human positive behavior. Neuroimaging studies suggest that the amygdala, orbitofrontal cortex, and ventral striatum are involved in reward prediction (30, 31). To select a different behavior from multiple behavioral options, the predicted rewards associated with each behavior must be compared and evaluated, and the behavior with the highest reward among the predicted rewards must be selected. Involvement of the orbitofrontal cortex has also been suggested for this selection (7). Given the involvement of the reward system in motivating behavioral choices, it appears that dysfunction of the reward system may make it difficult for subjects to motivate their behavior. In addition, the ventral tegmental area of the midbrain projects dopamine neurons to the striatum and prefrontal cortex, as well as to the amygdala and hippocampus, which are involved in emotion (32). From this perspective, FSN may be associated with depressive mood, a core symptom of depression. Loss of pleasure is a major symptom of MDD (33). However, a recent systematic review of fMRI-based studies indicates that impairment of the reward system, as indicated by hypoactivation of the striatum and blunted frontal lobe sensitivity, is associated with impaired reward processing in MDD (34). This suggests that impairment of the reward system is associated with depressive mood and loss of pleasure, which are core symptoms of depression.

However, the present study found no correlation between FSN and total HAMD-17 scores or individual item scores in MDD patients. MDD is a highly heterogeneous syndrome based on a complex pathology with a wide variety of phenotypes. Particularly, although the FSN plays an important role in the pathophysiology and symptoms of depression, it may also work in complex associations (or collaborations) with other neural networks to

TABLE 3 Effect of age and sex on FSN.

MDD				
	Estimate	Standard error	t Value	p Value
Age	0.002283	0.006306	-0.342	0.733
Sex	-0.157289	0.211776	-0.743	0.460
HC				
	Estimate	standard error	t value	p-value
Age	-0.56556	0.007161	-7.898	1.73e-11*
Sex	-0.186593	0.184593	-1.011	0.315

*Statistically significant (p<0.05).
MDD, major depressive disorder; FSN, fronto-striato network; HAMD-17, 17-item Hamilton Rating Scale for Depression.

create various phenotypes of depression. Our previous study found no significant differences in the salience, medial temporal lobe, default mode, medial temporal lobe, default mode, and central executive network between the MDD and HC groups (15). This could be one of the reasons for the lack of association with the total HAMD-17 score and each item score in the current study. The present results may reflect that the pathophysiology of depression is due to dysfunction of multiple brain networks and not only of the FSN (35). The association of brain structure and function with complex behaviors should be investigated in large-scale studies to ensure reliability (36). Considering the previous studies on the association between reward system network impairment and depressive symptoms, it is possible that the current study did not have an adequate sample size, which may have affected the results.

4.1 Limitations

This study had several limitations. As this was a cross-sectional study that enrolled a small number of patients, the temporal relationship between depressive symptoms and the frontal-basal ganglia network remains unknown. Some of the MDD subjects in this study received psychotherapeutic treatments such as cognitive-behavioral therapy and dynamic psychotherapy, and these treatments may have influenced the results. Considering that the relationship between brain structure and function and complex

TABLE 4 Effects of age, sex, and presence of depression on FSN.

	Estimate	Standard error	t Value	p Value
Age	-0.056486	0.007722	-7.315	1.47e-11*
Depression	-2.608625	0.436544	-5.976	1.62e-08*
Sex	-0.171657	0.139890	-1.227	0.222
Age: Depression	0.058825	0.009700	6.064	1.04e-08*

*Statistically significant (p<0.01).
MDD, major depressive disorder; FSN, fronto-striato network.

TABLE 5 Correlation between FSN and HAMD-17 total score/each item.

	Correlation coefficient	p Value
Total	-0.00545	0.962
Depressed mood	-0.261	0.0226
Feelings of guilt	-0.0902	0.438
Suicide	-0.191	0.0981
Insomnia - early	0.115	0.322
Insomnia - middle	0.196	0.0892
Insomnia - late	0.11	0.345
Work and activities	-0.28	0.0144
Retardation - psychomotor		
Agitation	0.0847	0.467
Anxiety - psychological	-0.117	0.314
Anxiety - somatic	0.0317	0.786
Somatic symptoms GI	-0.173	0.135
Somatic symptoms - General	0.146	0.208
Sexual dysfunction - menstrual disturbance	0.115	0.323
Hypochondria	0.33	0.00364
Weight loss by history	0.00895	0.939
Insight	0.184	0.111

p-Value adjusted by Bonferroni method=0.00278.
HAMD-17, 17-item Hamilton Rating Scale for Depression.

behavior should be investigated using large-scale studies to ensure reliability (36), the sample size was not sufficient in the current study. In addition, the FNS was determined through subjective visual assessment in the study subjects in whom the brain volumes were highly interlinked. Although the FSN is classified into five loop circuits (12, 13), it is unclear which circuit the present network falls into. Although the results indicated a significant difference in age between the HC and MDD groups, the analysis of the correlation between FSN and age in each group did not consider the imbalance in age between the two groups. This may have affected the conclusions. The current study did not obtain information on the duration of MDD symptoms. Although the disease duration would not be long because the patients only had their first episode and were untreated, the duration may still have influenced the results. In addition, although the frontal-basal ganglia network includes the nucleus accumbens and the prefrontal cortex, which are parts of the reward system, it may also include other areas that are not related to the reward system. Therefore, the representativeness of the frontal lobe-basal ganglia network as an evaluative value of the reward system has not been fully elucidated. In addition, the correlations were weak, and the present study intended to demonstrate correlations, not causality. Further studies are required to ascertain whether these correlations are clinically meaningful or therapeutically useful.

4.2 Conclusion

The function of the reward system is decreased in patients with MDD, and the extent of this decrease may be more pronounced in younger patients. Meanwhile, the overall severity of MDD and each severity are not related to the decline in reward system function. However, age may need to be taken into consideration. In addition, the usefulness of using the severity of the disease may need to be carefully judged. Further studies are needed to validate these findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan, Kitakyushu, Japan (approval number: H25-13). Informed consent was obtained from all subjects involved in the study.

Author contributions

RK: Conceptualization, Data curation, Formal Analysis, Investigation, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. KW: Writing – original draft, Writing – review & editing. NO: Methodology, Software, Validation, Writing – review & editing. AI:

Investigation, Software, Supervision, Writing – review & editing. HT: Investigation, Methodology, Software, Writing – review & editing. SK: Methodology, Software, Supervision, Writing – review & editing. RY: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Weakened effective connectivity between salience network and default mode network during resting state in adolescent depression

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Adolescent major depressive disorder (MDD) is associated with altered resting-state connectivity between the default mode network (DMN) and the salience network (SN), which are involved in self-referential processing and detecting and filtering salient stimuli, respectively. Using spectral dynamical causal modelling, we investigated the effective connectivity and input sensitivity between key nodes of these networks in 30 adolescents with MDD and 32 healthy controls while undergoing resting-state fMRI. We found that the DMN received weaker inhibition from the SN and that the medial prefrontal cortex and the anterior cingulate cortex showed reduced self-inhibition in MDD, making them more prone to external influences. Moreover, we found that selective serotonin reuptake inhibitor (SSRI) intake was associated with decreased and increased self-inhibition of the SN and DMN, respectively, in patients. Our findings suggest that adolescent MDD is characterized by a hierarchical imbalance between the DMN and the SN, which could affect the integration of emotional and self-related information. We propose that SSRIs may help restore network function by modulating excitatory/inhibitory balance in the DMN and the SN. Our study highlights the potential of prefrontal-amygdala interactions as a biomarker and a therapeutic target for adolescent depression.

KEYWORDS

adolescence, affective disorders, brain connectivity, resting-state fMRI, SSRI

1 Introduction

Major depressive disorder (MDD) is a common and debilitating condition with onset peaking in adolescence (1) which is estimated to have a lifetime prevalence of approximately 11% (2). Adolescent MDD exerts detrimental effects on physical and mental health, impairing academic, occupational, and social functioning. Additionally, it elevates the risk of recurrent MDD episodes in adulthood, co-occurring psychiatric and medical conditions, such as anxiety disorders, and suicide, the second leading cause of mortality in individuals aged 15 to 19 years (3, 4). The underlying neurobiological factors of the emergence and early trajectory of MDD in adolescence remain poorly understood, despite the known adverse consequences of this disorder.

Previous studies have reported several changes of large-scale functional brain networks in adult and adolescent depression. Large-scale networks are defined as a distributed set of brain regions that show a temporal correlation during a task or spontaneous thought (i.e., rest (5)). They are thought to support embedding predictions and prediction errors which dynamically adjust the brain's internal generative models based on sensory inputs and prior expectations (6, 7). These models have a hierarchical structure, meaning that higher-level processing regions generate predictions that are sent to lower-level regions, where they are compared with the incoming sensory data. The prediction error – the mismatch between predictions and data – is propagated back to the higher-level regions to update the models (7). During rest, it has been proposed that the dynamic fluctuations quantified as connectivity in large-scale networks represent an optimization of generative models for future interactions (8).

Multiple studies found that connectivity of the default mode network (DMN) is affected in MDD. Core nodes of the DMN, the medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC) have shown alterations in children and adults with or at risk for MDD (9–14). A recent longitudinal study linked altered developmental trajectory of DMN connectivity to depressive symptoms in youth (15), indicating that clinically relevant alterations manifest relatively early in brain development. In addition, there is compelling evidence that core nodes of the affective network (the amygdala) and the ventral attention network [dorsal anterior cingulate cortex, ACC (16)] – together forming the salience network [SN (17)] – show aberrant connectivity in adolescent (11, 18–22) and adult MDD (13, 14).

These alterations in large-scale networks are intriguingly aligned with the concepts of predictive processing and their potential role in the aetiology of depressive symptoms. It has been assumed that those network changes represent the neural manifestation of the predictive biases and altered perception characteristic of depression, further connecting the theoretical framework with the observed neurobiology (23, 24). As individuals with MDD tend to anticipate negative events more frequently than positive ones, the connectivity changes of core nodes of the DMN become crucial. The DMN's involvement in self-referential processing and its role in maintaining the most abstract

predictions of the internal models could contribute to the formation of these biased predictions (24–26). The SN's role in regulating attention (27) and encoding the relevance of both external and internal stimuli could in turn influence the selection of which sensory prediction errors to attend to by modulating the gain on prediction error signals originating from the sensory periphery (28). Additionally, aberrant connectivity within core nodes of the SN might amplify the attentional focus on (negative) prediction errors. This could lead to a vicious cycle where heightened sensitivity to negative information reinforces maladaptive perception.

Furthermore, the intricate interactions between these large-scale networks, as proposed by the triple-network model (29), might be pivotal in understanding the emergence and persistence of depressive symptomatology. Altered connectivity between these networks, not only underlie maladaptive self-referential processing and emotional regulation but also hinder the brain's ability to effectively update its internal model and adapt to external cues. This insensitivity to external cues, driven by skewed predictions and impaired network communication, likely contributes to the cognitive and emotional symptoms commonly observed in depression (24, 30). More specifically, altered amygdala function has been suggested to contribute to maladaptive weighting of relevance (i.e., loss of precision or heightened uncertainty about relevance) of incoming bottom-up signals in depression (19, 24, 28, 31). The resulting imprecision of bottom-up signals may entail failure of updating the internal model and their dismissal which may underlie symptoms such as rumination (24). In light of this, there is evidence of reduced connectivity between the amygdala and other SN regions in adolescent depression (32) which could indicate impaired detection and integration of relevant sensory signals that challenge the models' prediction. Altered connectivity between DMN and SN (e.g., the dorsal ACC, 16) could in turn be interpreted as altered precision over the predictions of the internal model, contributing to a “locked-in state” of negative thoughts (28). Altogether, current evidence suggests that the interactions between intrinsic brain networks, the DMN and the SN, might be closely linked to depression and contribute to the cardinal symptoms of rumination and negative mood.

The goal of the current study was to examine the functional integration of DMN and SN in adolescent depression. We used spectral dynamic causal modelling (spDCM; (33)) in the Parametric Empirical Bayes (PEB) framework to study the effective connectivity of the DMN and the important nodes of the SN during rest using multi-echo fMRI. Spectral DCM allows to model the directed relationships between brain networks and determines regions that are driving activity in other regions and their respective input sensitivity or excitatory-inhibitory balance (i.e., interregional self-inhibition or synaptic gain). In the predictive coding framework the excitatory-inhibitory balance reflects the precision of prediction errors encoded in the excitability of superficial pyramidal cells that is affected by both classical neuromodulators and inhibitory interneurons – lending the self-inhibition parameter to a straight-forward interpretation in terms of efficiency of information processing and network synchrony (i.e.,

a higher the self-inhibition reduces the influence of other regions) (34).

We investigated connectivity between the MPFC and PCC comprising the principal nodes of the DMN, and the dorsal ACC and bilateral amygdalae as part of the SN. The primary hypothesis of our study was that the effective resting-state connectivity between the amygdalae and the default mode network is altered in adolescents with MDD (14, 19). In addition, we hypothesised that the amygdalae show hypoconnectivity within the SN (32). Finally, we expected a decrease in the self-inhibition parameters of the spDCM, which regulate the excitatory-inhibitory balance of the regions. Such a decrease would lead to more excitability within the DMN regions, indicating aberrant encoding of precision (24, 33, 35).

2 Materials and methods

2.1 Participants

Thirty MDD patients and 32 healthy individuals matched for age, IQ, sex, and handedness participated in this study (Table 1). To assess the participants, a semistructured clinical interview was administered using either the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (Kiddie-SADS, 36) or the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID, 37). Criteria for the diagnosis of MDD in accordance with both the International Classification of Diseases (ICD-10) and the

TABLE 1 Clinical and demographic characteristics of study participants.

	Controls	MDD	Test statistic	p value ^a
Age (years), range (min-max)	16.2 (1.9), 11.2-18.8	16.1 (1.4), 12.8-18.7	U=553.5	.425
Sex (males), No. (%)	10 (30%)	10 (33%)	$\chi^2(1)=0.07$	.796
Handedness (right), No. (%)	32 (97%)	28 (93%)	$\chi^2(1)=0.46$	.500
In-scanner movement (FD, mm)	0.16 (0.06)	0.17 (0.06)	t(61)=0.69	0.492
CD-RISC	72.9 (10.1)	38.6 (15.6)	t(58)=10.16	<.001
CDI	8.4 (6.6)	29.6 (9.3)	U=38.0	<.001
Anhedonia	2.3 (2.2)	10.5 (2.8)	U=13.5	<.001
Negative mood	2.2 (2.0)	6.4 (2.4)	U=88.0	<.001
Negative self-esteem	1.0 (1.2)	5.0 (1.7)	U=42.0	<.001
Ineffectiveness	1.2 (1.2)	5.0 (1.9)	U=54.5	<.001
Interpersonal problems	1.1 (1.2)	3.7 (1.5)	U=74.5	<.001
Stomach	0.6 (0.6)	1.1 (0.8)	U=301.5	.018
RIAS IQ	104.5 (6.9)	108.0 (8.7)	t(60)=-1.75	.079
PSS	22.4 (6.6)	28.8 (7.7)	t(57)=-3.44	.001
SDQ	8.8 (5.3)	16.3 (5.6)	t(56)=-5.26	<.001
WISC-IV Digitspan (forward)	8.9 (2.1)	8.8 (2.0)	t(60)=0.32	.747
WISC-IV Digitspan (backward)	8.6 (1.6)	9.4 (2.0)	t(60)=-1.70	.094
WISC-IV Mosaic	57.0 (5.7)	59.0 (6.2)	t(56)=-1.27	.208
Current Medication, No. (%)				
No medication	NA	10 (33%)	NA	NA
SSRI	NA	18 (60%)	NA	NA
Dual-action antidepressant ^b	NA	2 (7%)	NA	NA
NERI	NA	2 (7%)	NA	NA
Antipsychotic ^c	NA	2 (7%)	NA	NA
Methylphenidate	NA	2 (7%)	NA	NA

Data are presented as mean (SD) if not indicated otherwise.
CD-RISC, Connor-Davidson Resilience Scale; CDI, Children Depression Inventory; FD, framewise displacement; RIAS, Reynolds Intellectual Assessment Scales; PSS, Perceived Stress Scale; SDQ-K, Strength and Difficulty Questionnaire for Children; WISC, Wechsler Intelligence Scale for Children.
^aUncorrected p values for between-group comparisons; significance threshold p<.05.
^bSerotonin-noradrenalin reuptake inhibitor.
^cUsed for behavioral control.

Diagnostic and Statistical Manual of Mental Disorders (DSM-5) were met by all patients, as determined by the Kiddie-SADS or MINI-KID, respectively. Inclusion criteria for study participation encompassed individuals within the age range of 8 to 18 years. Exclusion criteria encompassed any contraindication for magnetic resonance imaging (MRI) and, for the control group, the absence of any prevailing psychiatric axis-1 diagnosis. All participants gave their written informed consent and were financially reimbursed at the end of the study. Patients received psychotherapy as needed during the study. This study was approved by the ethics committee of the Canton of Zurich and was conducted in accordance with the Declaration of Helsinki.

2.2 Imaging and preprocessing

Image data acquisition was conducted on an Achieva 3T scanner (Philips Medical Systems, Best, the Netherlands) using a 32-channel head coil array. We acquired a T1-weighted structural scan of each subject [MP-RAGE, aligned at AC-PC, flip angle = 9° , voxel size = $1.05 \times 1.05 \times 1.2\text{mm}^3$, field of view = $270 \times 253\text{mm}^2$, 170 sagittal slices]. Subsequently, T2*-weighted images were acquired using a multi-echo multi-slice echo-planar images sequence [200 volumes per session, $TR = 2300\text{ms}$, $TE = 13,31,49\text{ms}$, 33 slices, voxel size = $3.75 \times 3.75 \times 3.79\text{mm}^3$, matrix size = $64 \times 64\text{px}$, flip angle = 80° , gap = 0.39mm , SENSE-factor = 2, MB-factor = 2] during a ~6 minute resting state with eyes open. During preprocessing, the volumes corresponding to the three echoes were separately despiked (`spmup_despike.m`, https://github.com/CPernet/spmup/wiki/spmup_despike.m) and slice-time corrected using SPM12. The motion parameters were calculated from the first echo and applied to the remaining echoes using `mcFLIRT` from the FSL toolbox (38). TEDANA, that is part of the Multi Echo Independent Component Analysis (MEICA) package [<https://afni.nimh.nih.gov/pub/dist/src/pkundu/meica.py> (39)], was used to perform state-of-the-art TE-dependent ICA-based denoising and T2* weighted averaging of optimally combined echoes and fully leverage all available data – particularly in ventral regions (40). The denoised images were coregistered to the structural scan and normalized to the Montreal Neurological Institute (MNI)-152 template space using the deformation fields derived from segmentation. Finally, we applied spatial smoothing using a 6mm full-width-half-maximum kernel to the functional images. Subsequently, a general linear model was created including the motion parameters and discrete cosine transform for band-pass-filtering (frequency range 0.08–0.01 Hz). An inspection of the mean framewise displacement (FD; 41) in patients and controls showed no evidence of differences in head motion between groups, $t(60) = 0.003$, $p = .99$, no individual subject showed a mean FD in excess of 0.27mm .

2.3 Timeseries extraction and statistical analysis

The coordinates for extraction of regional signals for the spDCM analysis were based on the literature (42, 43). We created

spherical search volumes ($r=8\text{mm}$) for the network nodes of the MPFC ($x=-1$, $y=54$, $z=27\text{mm}$ MNI) and the PCC ($x=0$, $y=-52$, $z=7\text{mm}$ MNI), the dorsal ACC ($x=0$, $y=21$, $z=36\text{mm}$ MNI), and the bilateral amygdalae (AMY; $x = \pm 19$, $y=-2$, $z=-21\text{mm}$ MNI). We centered the spherical ROI around each participant's maximum within the search volume and extracted the first eigenvariate of the time course of active voxels ($p < .05$, uncorrected). Realignment parameters obtained during preprocessing were partialled out.

We applied spectral dynamic causal modelling (spDCM) to estimate intrinsic effective connectivity from resting state fMRI data (44). SpDCM is a method that models the cross-spectra of the blood oxygenation level dependency (BOLD) signals, which are a more comprehensive measure of connectivity than the conventional zero-lag correlation. SpDCM allows us to determine the directed connectivity strengths between brain regions that drive their activity, as well as their input sensitivity or synaptic gain, which corresponds to the excitatory/inhibitory balance of each region.

We set up a fully connected model on all interregional connections. The analysis was conducted within the PEB framework where the full DCM model was estimated in an empirical Bayesian inversion scheme for each participant (45). Group effects on the DCM parameters (i.e., connectivity strengths) were analysed with a second-level PEB model to find group differences between patients and controls within the specified brain network. We used a Bayesian model reduction procedure to discard the model parameters not contributing to the model evidence in a greedy-search. This procedure stops when it removes a connection that decreases the model evidence. We analyzed the average intrinsic connectivity with group as predictor and sex, age, and handedness as covariates. To investigate potential effects of selective serotonin reuptake inhibitor (SSRI) intake in the eighteen patients on SSRIs, we added an additional regressor for SSRI intake to the PEB model. One patient was excluded from this analysis due to not disclosing their medication status. Group-level parameters were determined by averaging the best 256 nested models, weighted by their posterior probability. Parameters were considered significant when exceeding a 95% posterior probability of being present, based on the model evidence. As a last step, to validate our results, we used leave-one-out cross-validation (LOOCV; `spm_dcm_loo.m`) and assessed the predictive validity of the individual parameters of the connectivity model. To this end, we used the list of class probabilities for each subject and used it to retrieve the Receiver Operating Characteristic (ROC) curve and the Area Under the Curve (AUC) – the probability of a correct classification – with 95% confidence bounds across the cross-validation runs.

3 Results

3.1 Demographics and clinical symptoms

Patients and controls did not differ significantly in age, sex, IQ, handedness, or in-scanner movement ($p > .05$). They differed in clinical symptom scales: patients scored significantly higher on the Child Depression Inventory ($p < .001$), Connor-Davidson Resilience

Scale ($p < .001$), Perceived Stress Scale ($p = .001$) and the Strength and Difficulty Questionnaire ($p < .001$). In-scanner movement during the scan measured as framewise displacement did not differ between the groups ($p = 0.492$). Sample characteristics and test results are summarized in [Table 1](#).

3.2 Spectral DCM model structure across groups

The overall model structure across groups revealed by spDCM was primarily characterized by the directed negative coupling between SN

and DMN ([Table 2](#), [Figure 1A](#)). In particular, we found significant connectivity from the lAMY and PCC (expected value = -0.314 Hz, PP = 1.00) and MPFC (expected value = -0.234 Hz, PP = 1.00) and from rAMY to PCC (expected value = -0.425 Hz, PP = 1.00) and MPFC (expected value = -0.234 Hz, PP = 1.00). A unidirectional inhibitory connection from the ACC to the PCC portion of the DMN was also significant across both groups (expected value = -0.222 Hz, PP = 1.00). Connectivity within SN was characterized by functional coupling from the lAMY to rAMY (expected value = 0.234 Hz, PP = 1.00) and from the rAMY to the ACC (expected value = -0.149 Hz, PP = 1.00). Other connections were pruned from the model as they did not contribute significantly to the model evidence ([Table 2](#), [Figure 1A](#)).

TABLE 2 Connectivity strength (posterior probability) during resting state obtained by Bayesian model averaging of PEB model parameters.

Connection type	Common	MDD	SSRI	Sex	Age	Handed.
Endogenous parameters						
PCC→lAMY	–	–	–	–	–	–
PCC→rAMY	–	–	–	–	–	–
PCC→MPFC	–	–	–	–	–	–
PCC→ACC	–	–	–	–	–	–
MPFC→PCC	–	–	–	–0.080	0.058 (1)	–
MPFC→ACC	–	–	–	–	–	–
MPFC→lAMY	–	–	–	–	–	–
MPFC→rAMY	–	–	–	–	–	–
ACC→PCC	–0.222 (1)	–	–	–	–	0.198 (1)
ACC→MPFC	–	–	–	–	–	–
ACC→lAMY	–	–	–	–	–	–
ACC→rAMY	–	–	–	–	–	–
lAMY→PCC	–0.314 (1)	0.111 (1)	–	–0.09	–	–
lAMY→MPFC	–0.229 (1)	0.098 (1)	–	–	–0.061	–
lAMY→ACC	–	–	–	–	–	–
lAMY→rAMY	0.234 (1)	–	–	–	–	–
rAMY→PCC	–0.425 (1)	0.167 (1)	–	–	–	–
rAMY→MPFC	–0.234 (1)	0.094 (1)	–	–	–	–
rAMY→ACC	–0.149 (1)	–	–	–	–0.062 (1)	–
rAMY→lAMY	–	–	–	–	–	–
Self-inhibition parameters						
lAMY→lAMY	0.603 (1)	–	–	–	–	–
rAMY→rAMY	0.760 (1)	–	–	–	0.047 (1)	–
ACC→ACC	0.134 (1)	–0.217 (1)	–0.175 (1)	–	–	–
MPFC→MPFC	0.331 (1)	–0.119 (1)	0.128 (1)	0.107	–	–
PCC→PCC	–0.280 (1)	–	0.166 (1)	–	–	–

Between-region connections are in units of Hz. Self-inhibition parameters, where the source and target are the same, are the log of scaling parameters that multiply up or down the default value -0.5 Hz. Posterior probabilities are given in the brackets. $n = 61$. lAMY, left amygdala; rAMY, right amygdala; ACC, anterior cingulate cortex; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex.

“–” means “Pruned from the full model”.

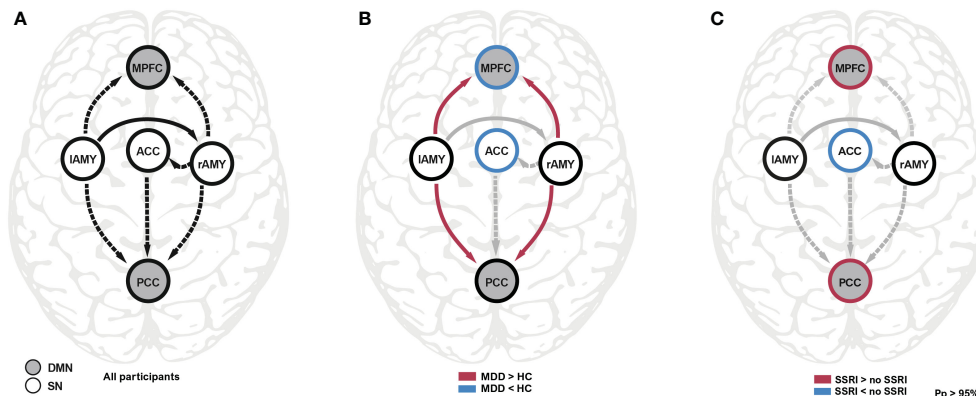


FIGURE 1

Spectral DCM analysis during resting state. **(A)** The common effect reflects the average connectivity and model structure across all participants. **(B)** Connectivity differences between controls and patients were found between amygdala and the core nodes of the DMN, as well as the self-inhibition parameters of MPFC and ACC. The latter regions were disinhibited (i.e. more sensitive to input) compared to healthy controls. **(C)** Patients taking SSRI showed decreased self-inhibition in the ACC and increased self-inhibition in the MPFC and PCC compared to patients not taking SSRIs. Detailed results are reported in Table 2. ACC, anterior cingulate cortex; DMN, default mode network; HC, healthy controls; IAMY, left amygdala; MDD, major depressive disorder; MPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; Pp, posterior probability; SSRI, selective serotonin reuptake inhibitor; rAMY, right amygdala; SN, salience network.

3.3 Aberrant connectivity from amygdala to default mode network in depression

We found evidence that connectivity in patients is significantly altered compared to healthy controls. Most prominently, the connections between bilateral amygdalae and both nodes of the DMN were affected (Figure 1B). Participants with MDD exhibited weaker inhibitory (more positive) connectivity between IAMY and DMN (MPFC: expected value of group difference = 0.098 Hz, posterior probability, PP = 1.00; PCC: expected value of group difference = 0.111 Hz, PP = 1.00), and rAMY and DMN (MPFC: expected value of group difference = 0.094 Hz, PP = 1.00, PCC: expected value of group difference = 0.167 Hz, PP = 1.00). Furthermore, the self-inhibition of both MPFC (expected value of group difference = -0.119, PP = 1.00) and ACC (expected value of group difference = -0.217, PP = 1.00) was decreased in patients. A LOOCV within the PEB framework showed that patients were identified significantly better than random classification [area under the curve, AUC = 0.76, 95% CI (0.62 0.86), Figure 2]. When performing an LOOCV for the individual parameters, the ACC self-connection [AUC = 0.73, 95% CI (0.59 0.84)] was a significant predictor for diagnostic status.

3.4 Connectivity for selective serotonin reuptake inhibitors

An exploratory analysis of effects of SSRI intake revealed that the self-inhibition of both nodes of the DMN increased (MPFC: expected value of difference = 0.128 Hz, PP = 1.00; PCC: expected value of difference = 0.166 Hz, PP = 1.00) whereas self-inhibition of the ACC in the SN decreased (expected value of difference = -0.175 Hz, PP = 1.00, Figure 1C). The lower this parameter, the more readily the region is excited by the network inputs, i.e., patients

receiving SSRIs during the study had increased input sensitivity in the ACC but decreased sensitivity in the DMN.

4 Discussion

The aim of this study was to compare brain connectivity of adolescents with MDD and matched healthy controls using spDCM during resting state. In our study cohort comprising 30 MDD

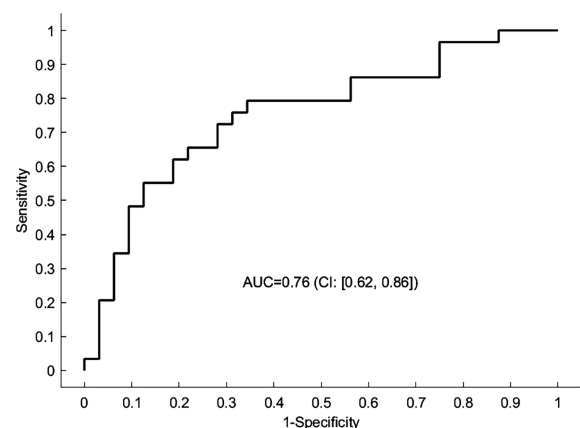


FIGURE 2

Predicting the diagnostic status using the spDCM connectivity parameters. The receiver operating characteristic (ROC) curve depicted here represents the outcome of a leave-one-out cross-validation procedure applied to the DCM analysis. The curve illustrates the trade-off between sensitivity and specificity for the predictive model across different thresholds. The area under the curve (AUC) serves as a statistical measure of the model's ability to correctly classify a new participant as having MDD or not. An AUC of 1 indicates perfect predictive accuracy, whereas an AUC of 0.5 suggests no discriminative power, equivalent to random chance.

patients, we conducted our analysis with a subset of 29 participants (excluding one patient), along with 32 healthy controls, as we examined the resting-state effective connectivity between principal nodes of the DMN and SN. Consistent with the growing literature that MDD is associated with a dysfunction of interactions of large-scale networks (46), our results indicate that altered effective connectivity within and between DMN and SN is a core feature of adolescent MDD. A leave-one-out cross-validation analysis showed that the effect size of DMN-SN interactions is sufficiently large to provide higher than chance prediction of diagnostic status in patients and healthy controls.

Corroborating our first hypothesis, we found that patients showed consistent weaker inhibition between the SN – particularly bilateral amygdalae – and the two principal nodes of the DMN (MPFC, PCC). This finding is in agreement with previous studies that report increased connectivity between the SN and the DMN in adult (9–14) and adolescent MDD patients (11, 18–22). Dysregulation of the affective brain during rest (i.e., weaker inhibitory bottom-up connectivity from SN to DMN) has been suggested to lead to excessive “emotional coloring” of thoughts and to symptoms such as rumination, negative affect, and an excessive self-focus (19). This is in line with the idea that altered large-scale network connectivity between the DMN and the SN is associated with maladaptive self-referential processing and emotional regulation in the triple-network model (29). Moreover, it has been suggested that depression is associated with differential integration of salience or precision signals (i.e., attentional control in the terms of predictive brain) in the brain (14). In particular, the amygdala is thought to carry information related to uncertainty about the predicted sensory input to the cortex (28, 31, 47, 48). In accordance with predictive processing theory, these results could therefore indicate that amygdala-DMN dysregulation reflect a failure to estimate the precision for incoming sensory data for allostatic regulation and thereby sustaining depressive symptoms (24). Although research is only beginning to unveil the underlying neurobiological mechanisms of predictive processing, our findings suggest that changes in amygdala-DMN connectivity play a pivotal role in adolescent depression in accordance with earlier work (11, 18, 19).

Second, our results show that patients had a weaker self-inhibition of the ACC. Reduced self-inhibition might be interpreted as loss of precision. The self-inhibition parameter indicates how strongly a region inhibits its own activity when it receives inputs from other regions. In conjunction with the overall inhibitory connection from the rAMY to the ACC, this is consistent with a previous functional connectivity study conducted by Pannekoek et al. (21), who reported increased negative connectivity between the rAMY and ACC. The ACC plays a pivotal role in visceromotor control, serving as a hub that can initiate appropriate actions when the brain detects sensory prediction errors arising from either external stimuli or the internal milieu (28). In this context, the stronger inhibition observed from the amygdala to the ACC in patients might be linked to altered processing dynamics of behavioral control. Specifically, a heightened inhibition could impede the ACC’s capacity to effectively detect and respond to prediction errors, which are crucial for guiding adaptive behavioral adjustments.

Besides the ACC, the MPFC also showed an increase in excitability in patients, exacerbating aberrant bottom-up influences from the amygdalae on its function.

The predictive coding theory posits that the excitatory-inhibitory balance primarily moderated by neuromodulatory systems and GABAergic interneurons governs the precision of prediction errors in the superficial pyramidal neurons within a hierarchical cortical network (6, 24). Prediction errors are signals that measure the mismatch between priors on upper levels and sensed information on lower levels, which are thought to be crucial for learning and updating internal models of the environment. By modulating the gain or excitability of superficial pyramidal cells within a region, self-connections modulate the precision of the prediction error. A loss of synaptic gain control in a given area could reduce the precision of information encoded within a region, and diminish its influence over lower level areas. In our model, this would correspond to a loss of influence (i.e., precision) of the more abstract priors in cortical high level areas (MPFC and ACC) over the more concrete bottom-up sensory data. Together with weaker amygdalar inhibition of the DMN, we suspect that imprecise prior beliefs will shift the weight in cortical updating to ascending autonomic information. In terms of this framework, this might represent a critical loss of precise encoding of uncertainty and would entail a model of the world that looks less predictable and more surprising – a take with remarkable parallels to the learned helplessness theory (49).

Interestingly, for patients who received SSRIs, self-inhibition in the ACC was further decreased compared to patients who did not receive SSRI treatment. This altered synaptic gain by SSRIs is believed to represent a mechanism by which SSRIs can improve clinical outcomes (50). By enhancing the excitability or sensitivity of the ACC to external input, such as from the amygdala, SSRIs may facilitate the learning and updating of internal models of the environment, and promote the resolution of uncertainties, facilitating the regaining of control over internal beliefs and reducing the weight on bottom-up signals. Moreover, patients who received SSRIs had comparable levels of self-inhibition in the MPFC to healthy controls, in contrast to patients who did not receive SSRI treatment. This observation may indicate restored synaptic gain and increased network efficiency in MDD patients, potentially aiding in regaining control over precision estimates of internal beliefs. A recent study of brain connectivity in adolescent MDD reported that SSRI treatment responders have a distinct connectivity profile compared to healthy controls and non-responders (11). Specifically, they exhibited greater DMN-SN inhibition (MPFC, ACC) and greater within-SN inhibition (amygdala, ACC), which appeared to facilitate the response to SSRI treatment. These findings suggest that brain connectivity could serve as a valuable marker for predicting and monitoring treatment response in MDD. However, the precise mechanisms and implications of SSRI-induced changes in brain connectivity remain unclear and warrant further investigation.

Given the complex interactions between the multiple neurotransmitter systems (e.g., serotonin, dopamine, GABA, glutamate) on the synaptic level, it is impossible to disentangle individual contributions with spDCM that investigates neuronal

ensembles. Nevertheless, several studies suggest reduction of GABA levels in the prefrontal cortex signalling in adolescent (51) and adult depression (52, 53). Animal studies show that the modulation of GABAergic interneurons can reestablish the excitation-inhibition balance (54) and that chronic SSRI treatment can stimulate the neurogenesis of GABAergic interneurons (55). Further evidence for this interpretation stems from the growing literature of ketamine in depression, that implicate the ACC as key target for the mood enhancing effect (56). Although the exact mechanism of antidepressant effect of ketamine remains unknown to date, it has been suggested that the blocking of NMDA receptor on GABA interneurons – and thereby attenuating GABA inhibition, which in turn leads to activation of pyramidal cells and promotes the release of brain-derived neurotrophic factor – might be critical for the alleviation of symptoms in adults (57) and adolescents (58). Yet, scrutinizing the individual contributions of neurotransmitters remains a difficult challenge, because of the intricate interactions on the synaptic level and multiple receptor subtypes expressed on GABAergic interneurons.

This study reveals new insights into the intrinsic brain connectivity in adolescents with MDD, however, it is not without limitations. Although our sample size is rather common for neuroimaging studies, it also reflects the recruitment challenges for this particular patient group. We used cross-validation procedures in our analysis to ensure the generalizability of results, nevertheless, future studies should replicate our results in larger cohorts to enhance the robustness of our findings and allow for more nuanced analyses. Second, to confirm clinical utility of these connectivity-based measures, longitudinal studies are required to study the change of symptoms alongside with changes in connectivity. The aforementioned study by (11) was the first to follow adolescent MDD patients to investigate treatment effects on effective connectivity longitudinally. Still, more studies that assess brain connectivity in parallel with treatment multiple times will be needed to understand the trajectories of symptoms in relation to neurobiological changes. Furthermore, in this study we focussed on the interactions between the DMN and the SN. Previous network models also implicate other large-scale networks (e.g. the cognitive control network, CCN, or reward network, RN) in depression (46). Understanding how neurodevelopmental trajectories between the DMN, SN, CCN, or RN affect mood will be pivotal for a comprehensive model of the disorder. Lastly, the scope of our study did not extend to the assessment of counseling interventions, which are distinct from psychotherapy in both accessibility and methodology. Future research should aim to include these interventions to better understand their potential in enhancing mental health outcomes.

In conclusion, this study sheds new light on the neurobiology of mechanisms in adolescent depression. We highlight the importance of the effective connectivity between – and within – DMN and SN during resting state in adolescent MDD. This connectivity pattern might represent a potential neurobiological marker of adolescent MDD and may be used to measure and predict depression. Our results suggest a new direction for studying mental health problems in adolescents and their respective treatments.

Data availability statement

All relevant anonymised data and codes used to generate results are available from the authors on request, subject to compliance with the requirements of the ethics committee of the Canton of Zurich, Switzerland.

Ethics statement

The studies involving humans were approved by Ethics committee of the Canton of Zurich, Switzerland. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

DW: Writing – original draft, Software, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. IH: Writing – review & editing, Investigation. II: Writing – review & editing, Software, Methodology. GB: Writing – review & editing, Resources, Investigation, Funding acquisition. SW: Writing – review & editing, Resources, Methodology. SB: Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Formal Analysis, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Hippocampal subfield morphology from first episodes of bipolar disorder type II and major depressive disorder in a drug naïve Chinese cohort

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Introduction: Symptoms during the onset of major depressive disorder [MDD] and bipolar disorder type II [BD-II] are similar. The difference of hippocampus subregion could be a biological marker to distinguish MDD from BD-II.

Methods: We recruited 61 drug-naïve patients with a first-episode MDD and BD-II episode and 30 healthy controls (HC) to participate in a magnetic resonance imaging [MRI] study. We built a general linear model (one-way analysis of covariance) with 22 hippocampal subfields and two total hippocampal volumes as dependent variables, and the diagnosis of MDD, BD-II, and HC as independent variables. We performed pair-wise comparisons of hippocampal subfield volumes between MDD and HC, BD-II and MDD, BD-II and HC with *post hoc* for primary analysis.

Results: We identified three regions that differed significantly in size between patients and controls. The left hippocampal fissure, the hippocampal–amygdaloid transition area (HATA), and the right subiculum body were all significantly larger in patients with MDD compared with the HC. In the onset of first-episode of MDD, the hippocampal volume increased significantly, especially on the left side comparing to HC. However, we found differences between MDD and BD-II were not statistically significant. The volume of the left HATA and right subiculum body in BD-II was larger.

Conclusions: The sample size of this study is relatively small, as it is a cross-sectional comparative study. In both MDD and BD-II groups, the volume of more left subregions appeared to increase. The left subregions were severely injured in the development of depressive disorder.

KEYWORDS

BD-II, MDD, hippocampus, subregions, magnetic resonance imaging

1 Introduction

The characteristics of depressive episodes of bipolar disorder type II [BD-II] are very similar to those of a major depressive disorder [MDD]. However the prevalence of BD-II is 4.5% less than that of MDD (16.2%) (1) and easily misdiagnosed in early episodes (2). The difficulty in identifying the first episode of depression in BD-II increases the possibility of misdiagnosis (2, 3). This misdiagnosis affects the choice of treatment options, and BD-II depressive episodes are often accompanied by anxiety characteristics and a high risk of self-injury and suicide (4, 5). If a depressive episode of BD-II is misdiagnosed as a depressive episode of MDD and then they were prescribed antidepressants, it can lead to mixed episodes or manic episodes, increasing the risk of suicide (6, 7). Therefore, early identification of depressive episodes of BD-II and intervention are very important. Exploration of the biological markers of BD-II lays the foundation for early diagnosis and intervention (8). Being able to distinguish BD-II from MDD early in the course of the disease would allow the provision of appropriate and effective treatment (9, 10). In this paper we set out to find biomarkers that would distinguish BD-II from MDD.

We chose to examine the hippocampus because of earlier findings suggesting that the size of the hippocampus might alter with changes in mood, and that cellular and molecular mechanisms associated with mood disorders were localised to specific hippocampal subfields (11). The hippocampus has important functions in the regulation of emotion and declarative memory (12). It has been shown that the volume of the hippocampus is smaller in MDD (13–18) and also smaller in bipolar disorder (19, 20). However, few studies have compared hippocampal substructures in MDD with BD-II depression (21, 22). A series of articles including Cao et al., and an ENIGMA Consortium study found that hippocampal volume was significantly reduced and changed in patients with bipolar disorder type I [BD-I] (11, 23, 24) or in a bipolar disorder affected group including BD-I and BD-II (25). However, there are few articles exploring specifically BD-II depressive episodes which are similar to episodes of MDD. Exploring the differences between these is very important and leads to an exploration of important markers for differentiation.

Some researchers found that hippocampal subfield volume reductions were more prominent in patients with MDD than with BD-II (26), while others found patients with BD-II had reduced volumes of the hippocampal subfields compared with those with MDD, especially in the left CA4, GCL, ML and both sides of the hippocampal tail (11). Furthermore, the duration of bipolar disorder was negatively correlated with the volume of the hippocampal subfields, which evidenced the neuroprogressive nature of BD-II (24, 26). The specific reduction of the hippocampal subfield in MDD is found in the cornu ammonis and dentate gyrus (27). The differences of hippocampal subfields between MDD and BD-II are helpful in understanding hippocampal neuroplasticity in them (27) and in discriminating them through structural MRI data (28).

Some researchers believe that BD-II is a progressive neurodegenerative change (Schneider, DelBello et al., 2012; Abe, Ching et al., 2022) and bipolar disorder progresses at the same time

as the volume of the hippocampus shrinks (Cao, Bauer et al., 2016 (29). For BD-II, the CA1 area in the hippocampus is believed to be reduced, which may be an important sign of severe mental disorder (30). However, in these studies, the fact that patients were undergoing treatment and the severity of the disorder were not considered, and the recurrence of the disorder and the specific type of BD were often regarded as unimportant factors, with notably few studies exploring the impact of the early development stage of BD-II on the hippocampus.

In this paper we hypothesize that: 1). We hypothesize that patients with BD-II will have same changes in the volume of left hippocampus as in patients with MDD comparing to controls. 2) There may be differences in the brain structure of patients with BD-II compared with patients with MDD. 3) Specifically, we asked whether for BD-II there may be less dominant reduction in some subregions of the hippocampus, such as cornu ammonis 1 [CA1] or granule cell-molecular layer-dentate gyrus [GC-ML-DG].

2 Methods

2.1 Participants

A total of 30 patients with the first episode of BD-II depression (18–60 years old), and 28 patients with the first episode of MDD (18–60 years old) were recruited from the Shanghai Mental Health Center, in Shanghai, in the People's Republic of China between January and December 2021. Using the patient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) patients were evaluated to see whether they met the diagnostic criteria for of BD-II and MDD(Those patients with BD-II currently have moderate or severe depressive symptoms. When reviewing their medical history, they have had mild manic episodes and were diagnosed with bipolar disorder. At the time of enrollment, the patients were still experiencing depressive symptoms.). Before the patients were further evaluated, their clinical symptoms were assessed according to the 24-item Hamilton Depression Rating Scale [often abbreviated to HDRS, HDRS or Ham-D] (31) and Hypomania Checklist [HCL-32] (32) but only for BD-II. The diagnosis was reviewed by an attending psychiatrist and deputy chief-psychiatrist to confirm that the diagnosis was consistent. For bipolar disorder, only patients with BD-II depression were enrolled. Inclusion criteria: age 18–60 years, right hand-dominant, meeting DSM-IV diagnosis criteria for MDD or BD-II; and drug-naïve patients with first-episode depression; for MDD patients, a total HDRS score of >20, and for BD-II, an HCL-32 score of >13 and an HDRS score of >20. Exclusion criteria: 1) Patient history of another DSM-IV Axis I disorder (e.g. schizophrenia, schizo-affective disorder or mental retardation). 2) Serious or unstable physical diseases such as tumours or cardiovascular disease, alcohol/substance abuse or any other severe physical disease. 3) Primary neurological diseases such as vascular disease or cognitive impairment. 4) Contraindications for MRI scanning including metal implants, dental braces or fear of claustrophobia. 5) Being in receipt of medication or physical therapy before enrolment. HC were age-matched and their HDRS score was checked to ensure that it was < 20 at the time recruitment

advertisements were put up in the community by the study doctor coordinating the case group. HCs needed to meet the following criteria: 1) 18–60 years old. 2) Met the criteria of the non-patient edition of the Structured Clinical Interview for DSM-IV Axis Disorders (SCID-NP). 3) They were not suffering from any current or past physical disease. 4) They had no family history of psychiatric illness. Everyone who participated in the study completed the informed consent form correctly. The project was approved by the Ethics Committee of the Shanghai Mental Health Center (approval No. 2020-55). The study was conducted according to the ethical principles set out in the World Medical Association's (WMA) Declaration of Helsinki.

2.2 Image acquisition

MRI images were acquired for all subjects using a 3T scanner (MAGNETOM Verio; Siemens Healthineers, Erlangen, Germany) using a 32-channel head coil at the Shanghai Mental Center. A foam pad was put under the patient's head to prevent head movement. Structural images were acquired using a whole-brain three-dimensional sagittal T1-weighted scan, with the following parameters: sagittal acquisition; repetition time/echo time: 2300 ms/2.96 ms; inversion time: 900ms; flip angle: 9°; field of view: 256×256 mm; resolution: 1 × 1 mm; slice thickness: 1 mm (isotropic voxel of 1 mm).

2.3 Image processing

A T1-weighted image performed visual quality control on artefacts, preprocessing by the standard Recon-all pipeline overview implanted in FreeSurfer v7.0. We used the automatic procedures of hippocampal subfield segmentation and volumetric measurements of participant T1 images developed by T1-weighted MRI. The volume of hippocampus was further pre-processed using the standard FreeSurfer recon-all pipeline (version 7.0) (<https://surfer.nmr.mgh.harvard.edu/fswiki/HippocampalSubfieldsAndNucleiOfAmygdala>) (33). The hippocampus is divided into twenty-two subregions: the hippocampus proper, the hippocampal head, the hippocampal tail, subiculum head and body, cornu ammonis 1 body and head, parasubiculum, presubiculum body and head, cornu ammonis 2/3 body and head (CA2/3-body, CA2/3 head), cornu ammonis 4 body and head (CA4-body, CA4 head), granule cell-molecular layer-dentate gyrus (GC-ML-DG) body and head (GC-ML-DG-body, GC-ML-DG-head), the molecular layer hippocampus body and head (molecular-layer-HP-body and head), hippocampal-amygdaloid transition area (HATA), fimbria. Before further analysis, the hippocampal volume was corrected relative to intracranial volume (ICV).

2.4 Statistical analyses

IBM SPSS statistics for Windows, Version 19.0 (Armonk, NY, USA) was used for analysis of demographic and volume of subregions of the hippocampus.

We built a general linear model (one-way analysis of covariance) approach with the following variables: 42 hippocampal subfields and two total hippocampal volumes as dependent variables, and the diagnosis of MDD, BD-II, HC as an independent variable; the variables of age, sex, and total intracranial cavity volume (TICV) were covariates. We performed the pair-wise comparisons of hippocampal subfield volumes between MDD and HC, BD-II and MDD, MDD and BD-II with *post hoc* for primary analysis. The Bonferroni correction for this analysis and *post-hoc* pair-wise comparisons was applied to minimize type-1 error risk ($P < 0.05/44 = 0.001136$). For demographic and clinical characteristics, we used an independent samples t-test to get the difference of HDRS, HCL-32 and family salary between MDD and BD-II. We applied the chi-squared tests on the distribution of sex of the MDD and BD-II group.

3 Results

3.1 Demographic data and characteristics

A total of 91 subjects (25 subjects with MDD, 36 with BD-II and 30 with healthy controls) was recruited to this study. Information regarding the sex, age, and other demographic features of subjects is given in Table 1. There were no significant differences in age ($P = 0.052$) or gender ($P = 0.117$) between MDD and BD-II. However, there was a significant difference in depressive symptom scores ($P = 0.019$) and HCL-32 scores ($p = < 0.001$) between MDD and BD-II (Table 1).

3.2 Hippocampal subfield volume differences between BD-II and healthy controls

Table 2 lists the regions we examined and shows results for comparisons between healthy controls and patients with BD-II. We tested 22 regions on the left side and the right side, as well as the total volume of the hippocampus. Although many of these measurements are correlated, we decided to treat each test as an independent analysis and thus set a Bonferroni corrected 5% significance threshold of $P = < 0.001$ ($0.05/44$). We found that 2 results exceeded this threshold including the left HATA and right subiculum body.

3.3 Hippocampal subfield volume differences between MDD and healthy controls

Table 2 shows results of comparisons between patients with MDD and HC. Since the measurements are the same as those collected for the analysis of BD-II, we applied the same significance thresholds. We found 3 results that exceeded the Bonferroni corrected threshold. We observed a significantly larger volume of

TABLE 1 Demographic information for all participants.

		N	Mean	Standard deviation	t	P-value
HAMD	MD	25	35.440	10.508	2.416	0.019
	BD II	36	28.583	11.165		
HCL-32	MD	25	9.960	2.879		<0.001
	BD II	36	23.056	6.155		
Age	MD	25	25.240	5.532	-1.984	0.052
	BD II	36	28.610	7.129		

P-values for age, HAMD, and HCL-32 scores were obtained using an independent t-test.
BD: bipolar disorder; MDD: major depressive disorder; Ham-D: 24 item Hamilton Depression Scale; HCL-32: Hypomania Check List.

the left hippocampal fissure and left HATA and the right subiculum body in MDD compared with the HC (Figure 1).

3.4 Hippocampal subfield volume differences between MDD and BD-II

We found no significant differences in any hippocampal measure between MDD, and BD-II.

4 Discussion

4.1 Summary of main findings in this study

We studied the difference of the hippocampal substructure between MDD and BD and HC, and compared the hippocampal substructure between MDD and BD-II. We found that a) in the BD-II, the hippocampal volume of the left HATA and right subiculum body was significantly increased. b) In MDD, the volume of the left hippocampal fissure, left HATA and right subiculum-body increased significantly. c) We found no significant difference in hippocampal substructure between MDD and BD-II.

4.2 Comparison with previous studies

When comparing the volume of the hippocampus in MDD to HC, most studies found that the volume is reduced (13, 17, 34, 35). We found that the volume of left HATA and right subiculum-body increased in patients with MDD (36). Previous studies have found that the left hippocampus is more reduced (36, 37), and we had similar findings showing that the left hippocampal body and the left HATA are most influenced. Yao found that subiculum and CA1 subregions of the bilateral hippocampus are prone to atrophy (17). Some researchers found a reduction in the volume of the hippocampal tail bilaterally, right hippocampal head and right hippocampus proper in MDD patients (14), showing that the right hippocampus is influenced too. However, most studies included patients with long term depression, or who were in

remission. Previous studies have found that the volume of the left hippocampal protrusion decreased after the first or repeated episodes of MDD (13). Few studies involved the first episode of MDD with drug naïve patients. We found that an increase in the left hippocampal fissure, left HATA and right subiculum-body of the hippocampus might be characteristic of early-stage depression.

For BD-II, in this study we found that more subfields of the hippocampus are influenced from the left side to the right side, including the left HATA and right subiculum body, findings which are similar to previous studies. Some researchers found that the most affected sizes were in volume differences between BD-II and HC in the molecular layer, the hippocampal tail, cornu ammonis (CA4), and cornu ammonis (CA1) (11, 19). There are specific changes in subregions of the hippocampus in depressive episodes of bipolar disorder, such as cornu ammonis 1 (CA1), cornu ammonis 4 (CA4) (11, 30), the granule cell layer (GCL), molecular layer (ML), subiculum (sub). However, one study found that the volume of these subregions was increased, perhaps because of confounders such as medication, alcohol and illicit substance use, illness stage and the age of onset (19). Cao et al., recruited BD-I and BD-II disorder patients who were receiving treatment (11). They found that patients with BD (including BD-I and BD-II), had reduced volumes of hippocampal subfields, specifically in the left CA4, GCL, ML and both sides of the hippocampal tail, compared with healthy subjects. Another study recruited adolescent BD patients with adult BD, and found no reduction in the size of the hippocampus (38). They recruited subjects who were mainly young people with BD-II. Although some researchers found that BD-I has a severer reduction in hippocampal subfields than BD-II (11, 30), we still need to pay attention to the confounding effects on the hippocampus of the disease episode, progression and medicine treatment. Our study found that BD-II produced an increase in the volume of left HATA and right subiculum body of the hippocampal subregions in the early stage particularly with drug-naïve and young patient groups.

We did not find any difference between MDD and bipolar disorder. Cao found that the hippocampal subfields were more affected in BD-I compared with BD-II and MDD (11). Kyu-Man Han et al., found similar results and showed that no significant volume differences were observed between MDD and BD (26). Kyu-Man Han’s study only recruited subjects who were euthymic or in a

TABLE 2 Hippocampal Differences between MDD,BD-II and healthy controls.

	All groups		BD vs HC		MDD vs HC		MDD vs BPD	
	F	P	t	P	t	P	t	P
Hippocampal tail L	0.807	0.45	1.178	0.243	0.916	0.364	0.134	0.894
Subiculum body L	3.543	0.033	1.809	0.075	2.69	0.01	-0.843	0.403
CA1 body L	5.791	0.004	2.606	0.011	3.097	0.003	-0.73	0.468
Subiculum head L	0.773	0.465	-0.093	0.926	1.04	0.303	-1.069	0.289
Hippocampal fissure L	7.733	0.001	2.475	0.016	4.657	<0.001	-1.546	0.127
Presubiculum head L	3.869	0.025	0.587	0.559	2.479	0.018	-2.057	0.044
CA1 head L	2.154	0.122	0.401	0.69	2.083	0.042	-1.551	0.126
Presubiculum body L	1.283	0.282	0.291	0.772	1.535	0.131	-1.332	0.188
Parasubiculum L	1.903	0.155	1.417	0.161	1.86	0.068	-0.643	0.522
Molecular layer HP head L	1.138	0.325	0.372	0.711	1.555	0.126	-1.08	0.284
Molecular layer HP body L	5.548	0.005	2.515	0.014	3.168	0.003	-0.67	0.505
GC ML DG head L	1.714	0.186	1.522	0.133	1.753	0.085	-0.284	0.778
CA3 body L	3.045	0.053	2.191	0.032	1.819	0.075	0.651	0.518
GC ML DG body L	2.207	0.116	1.96	0.054	1.685	0.098	-0.134	0.894
CA4 head L	1.819	0.168	1.499	0.139	1.806	0.077	-0.438	0.663
CA4 body L	1.788	0.173	1.771	0.081	1.469	0.148	0.068	0.946
Fimbria L	1.28	0.283	0.101	0.92	1.639	0.107	-1.316	0.193
CA3 head L	2.368	0.1	1.909	0.061	1.956	0.056	-0.055	0.956
HATA L	14.616	<0.001	4.116	1.21E-04	5.948	<0.001	-1.526	0.132
Whole hippocampal body L	5.167	0.008	2.214	0.03	3.167	0.003	-1.019	0.312
Whole hippocampal head L	2.496	0.088	1.008	0.317	2.413	0.019	-1.297	0.2
Whole hippocampus L	3.39	0.038	1.632	0.108	2.666	0.01	-1.066	0.291
Hippocampal tail R	1.543	0.219	1.434	0.156	1.472	0.147	-0.216	0.83
Subiculum body R	9.296	<0.001	3.423	1.09E-03	4.455	<0.001	-0.564	0.575
CA1 body R	2.605	0.08	1.763	0.083	1.987	0.052	-0.614	0.542
Subiculum head R	1.346	0.266	-0.577	0.566	1.003	0.32	-1.606	0.114
Hippocampalfissure R	2.07	0.132	0.257	0.798	2.062	0.044	-1.6	0.115
Presubiculum head R	2.341	0.102	0.985	0.328	2.08	0.042	-1.306	0.197
CA1 head R	0.683	0.508	0.646	0.52	1.136	0.261	-0.615	0.541
Presubiculum body R	2.419	0.095	0.683	0.497	2.113	0.039	-1.58	0.119
Parasubiculum R	5.585	0.005	2.661	0.01	3.301	0.002	-1.032	0.306
Molecular layer HP head R	1.04	0.358	0.481	0.632	1.367	0.177	-1.019	0.312
Molecular layer HP body R	3.758	0.027	2.021	0.047	2.563	0.013	-0.737	0.464
GC ML DG head R	1.376	0.258	1.048	0.299	1.647	0.106	-0.708	0.482

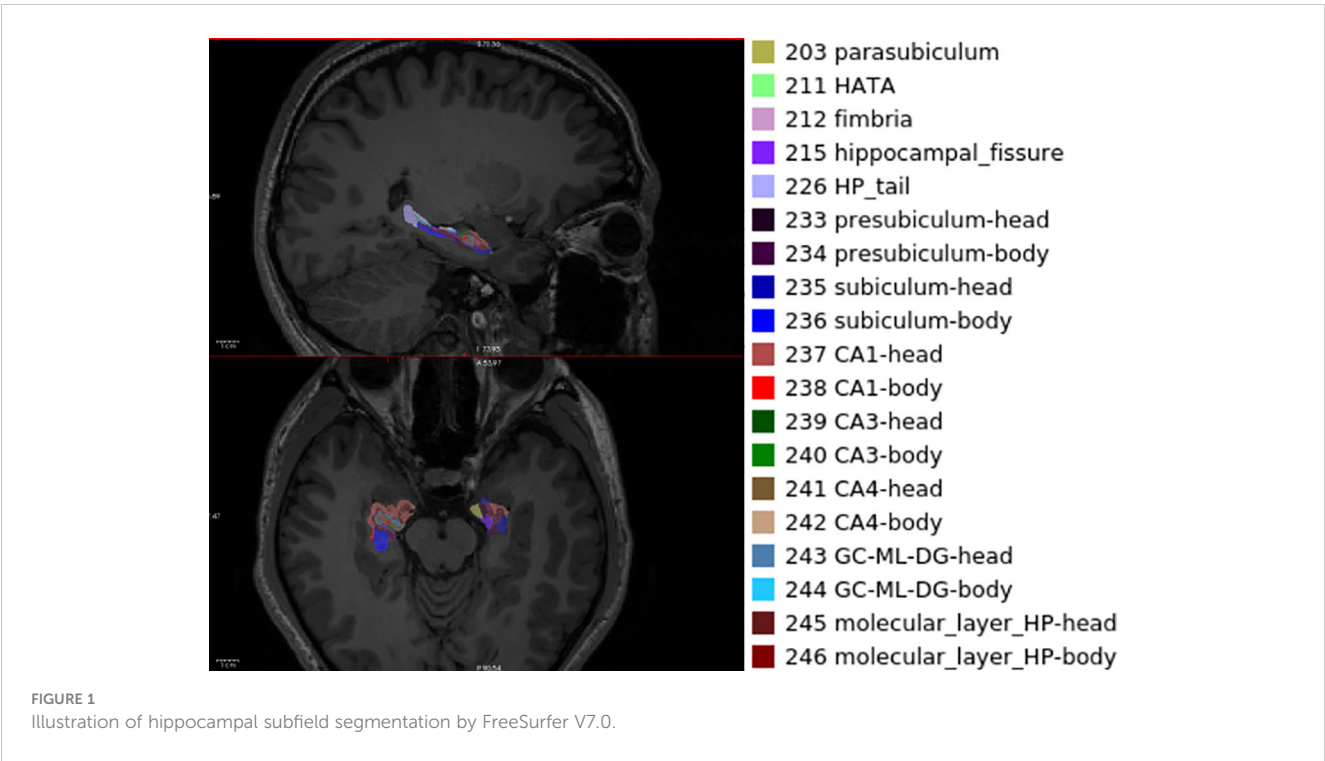
(Continued)

TABLE 2 Continued

	All groups		BD vs HC		MDD vs HC		MDD vs BPD	
	F	P	t	P	t	P	t	P
CA3 body R	0.256	0.775	0.685	0.496	0.541	0.59	0.042	0.966
GC ML DG body R	0.95	0.391	1.071	0.288	1.24	0.22	-0.386	0.701
CA4 head R	1.357	0.263	1.137	0.26	1.621	0.111	-0.589	0.558
CA4 body R	0.29	0.749	0.37	0.713	0.744	0.46	-0.446	0.657
Fimbria R	1.11	0.334	1.665	0.101	0.86	0.394	0.417	0.678
CA3 head R	1.868	0.16	1.338	0.186	1.893	0.064	-0.727	0.47
HATA R	2.904	0.06	1.489	0.142	2.436	0.018	-1.073	0.288
Wholehippocampal body R	4.724	0.011	2.267	0.027	2.976	0.004	-0.799	0.427
Whole hippocampal head R	1.695	0.19	0.868	0.389	1.822	0.074	-1.086	0.282
Whole hippocampus R	2.993	0.055	1.626	0.109	2.371	0.021	-0.935	0.353
Hippocampal tail L	0.807	0.45	1.178	0.243	0.916	0.364	0.134	0.894
Subiculum body L	3.543	0.033	1.809	0.075	2.69	0.01	-0.843	0.403

Bonferroni correction was applied: $P < 0.05/44 = 0.001136$.
Significant hippocampal subfield volume differences appear in bold.
MDD, major depressive disorder; BD, bipolar disorder; HC, healthy controls; CA, cornu ammonis.

depressive state. Another difference is that their study was conducted on patients with BD including BD-I and BD-II, who were already taking medicine (26). BD-I and BD-II may have different effects on the volume change of the hippocampus, so we should treat them differently. It is possible that the type of bipolar disorder, the effects of medicine, the episode and duration of the illness, and the number of episodes may affect the size of the hippocampus (11). In future, it will be necessary to compare the



differences in the hippocampus in the early, middle and multiple episodes of BD-II seen in this study.

4.3 Implications

Although we found no significant difference between BD-II and MDD in the hippocampal subregions, there were more extensive changes on the left side in MDD. One implication is that there is more extensive cognitive impairment during the onset of MDD, such as decreased working memory (39, 40) and episode memory. Some studies show that the cognitive dimension of MDD is more extensive.

This study only compares the symptoms of MDD and BD-II, and in doing so it found significant differences. It attempts to explore the differences in symptom-related hippocampal subregions. However, no significant difference was seen in the subregion of the hippocampus between the two diseases. Analysis of the results suggests that: the sample size is relatively small, and that we need to expand the sample to explore whether there is a linear relationship between the more serious depressive symptoms and the smaller hippocampal volume in MDD. In BD-II, there is no such linear relationship.

Our study recruited subjects with the first onset of depression and BD-II, and our findings suggest that the increase of hippocampal volume may be an early pathological change. Many studies are based on the hippocampal contractile changes of recurrent or mixed episodes of bipolar disorder (11, 26). Our study suggests that changes in hippocampal enlargement may be related to inflammatory response (41, 42) in the early stage of the disease. Moreover, the inflammatory response of MDD may be more obvious, which needs more basic research to see whether this is so.

4.4 Limitations

Our study had the following limitations: 1) our power to detect an effect is limited by our small sample size. In a recent large meta-analysis of imaging data from patients with MDD, Schmaal et al. (43) estimated that 545 subjects per group would be needed to provide 80% power to detect difference in hippocampal volume at P -value=0.05. At this point we can only caution that ours is an exploratory study, generating hypotheses for further investigation. 2) Our subjects were not matched for gender; Bipolar I is more common in men, while BD is more common in women (44). 3) Mixed episodes or rapid cycling of bipolar disorder is more likely to increase the risk of suicide, and such episodes cannot be evaluated. In this study, we did not assess whether patients with bipolar disorder had more frequent episodes or mixed episodes of BD, and which kind of clinical characteristics of bipolar disorder II were more likely to develop mixed episodes. 4) This study is cross-sectional. Only 20% of patients with bipolar disorder depressive episodes were diagnosed with bipolar disorder in the first year, and

the diagnosis was often delayed for 5-10 years (45). This is possible because a diagnosis of BD is difficult to make early in the course of the disorder. In this study, the patients with first-episode MDD before the age of 30 could not be ruled out from BD-II. It will be necessary to conduct follow-up studies on patients with MDD to see if they develop BD in the next 5-10 years. 5) Hippocampal volume has a close relationship with cognition. This study did not include level of education as a covariate, and follow-up studies need to comprehensively assess the impact of this. 6) The age of onset and the prolonged duration of the disorder are not included in the current study and should be discussed in future studies as influencing factors. 7) the diagnostic system in this study used DSM-IV, and it should be updated in the future study and the related psychotherapy situation could be recorded when the participants were interviewed. 8) A limitation of this study is that it examined only the hippocampus. Future work should study more extensively the brain regions involved in regulating emotional stability.

5 Conclusion

From the data in this study, it can be concluded that there is no significant difference in subregions of the hippocampus between BD-II and MDD in the early development of BD-II. In the early stage of MDD, the volume of the hippocampal subregions including the left hippocampal fissure, left HATA and right subiculum-body regions are increased, possibly influencing working memory and episodic memory.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Shanghai Mental Health Center (batch number: 2020-55). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

EC: Funding acquisition, Project administration, Resources, Writing – original draft. YZ: Data curation, Investigation, Methodology, Writing – review & editing. MW: Data curation, Investigation, Writing – review

& editing. HC: Data curation, Investigation, Writing – review & editing. YC: Data curation, Investigation, Writing – review & editing. ZL: Data curation, Investigation, Writing – review & editing. YW: Data curation, Investigation, Writing – review & editing. HW: Data curation, Investigation, Writing – review & editing. YH: Data curation, Investigation, Writing – review & editing. HZ: Data curation, Investigation, Writing – review & editing. YL: Data curation, Investigation, Writing – review & editing. XL: Data curation, Investigation, Writing – review & editing. PZ: Data curation, Investigation, Writing – review & editing. WL: Data curation, Investigation, Writing – review & editing. YX: Project administration, Supervision, Writing – review & editing. YW: Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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