Functional connectivity of the default mode network subsystems in patients with major depressive episodes with mixed features

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ABSTRACT

Background The neuroimaging mechanism of major depressive episodes with mixed features (MMF) is not clear.

Aims This study aimed to investigate the functional connectivity of the default mode network (DMN) subsystems among patients with MMF and patients with major depressive disorder without mixed features (MDD_{noMF}).

Methods This study recruited 47 patients with MDD_{noMF} and 27 patients with MMF from Beijing Anding Hospital, Capital Medical University, between April 2021 and June 2022. Forty-five healthy controls (HCs) were recruited. All subjects underwent resting-state functional magnetic resonance imaging scanning and clinical assessments. Intranetwork and internetwork functional connectivity were computed in the DMN core subsystem, dorsal medial prefrontal cortex (dMPFC) subsystem and medial temporal lobe (MTL) subsystem. Analysis of covariance method was performed to compare the intranetwork and internetwork functional connectivity in the DMN subsystems among the MDD_{noMF}, MMF and HC groups.

Results The functional connectivity within the DMN core (F=6.32, p_{FDR}=0.008) and MTL subsystems (F=4.45, p_{FDR}=0.021) showed significant differences among the MDD_{noMF}, MMF and HC groups. Compared with the HC group, the patients with MDD_{noMF} and MMF had increased functional connectivity within the DMN MTL subsystem, and the patients with MMF also showed increased functional connectivity within the DMN core subsystem. Meanwhile, compared with the MDD_{noMF}, the patients with MMF had increased functional connectivity within the DMN core subsystem (mean difference (MDD_{noMF}−MMF)=−0.08, SE=0.04, p=0.048). However, no significant differences were found within the DMN dMPFC subsystem and all the internetwork functional connectivity.

Conclusions Our results indicated abnormal functional connectivity patterns of DMN subsystems in patients with MMF, findings potentially beneficial to deepen our understanding of MMF's neural basis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Major depressive disorder (MDD) patients exhibited abnormal functional connectivity in the default mode network (DMN).
⇒ The resting-state functional connectivity patterns of the DMN subsystems in MDD patients with mixed features (MMF) are unclear.

WHAT THIS STUDY ADDS

⇒ The functional connectivity within the DMN core subsystem was significantly increased among the MMF patients compared with MDD patients without mixed features (MDD_{noMF}) and healthy controls (HCs).
⇒ The functional connectivity within the DMN medial temporal lobe (MTL) subsystem was significantly increased both in the MMF patients and MDD_{noMF} patients compared with HCs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results indicated that the disrupted DMN subsystem might be associated with the pathophysiology of MMF patients.

lower response to them, increased risk for relapse, suicide, increased psychiatric comorbidities, poorer functioning and lower quality of life.[1] Nearly one-third of patients with major depressive disorder (MDD) present mixed features.[2] Moreover, MMF has a high risk for developing into bipolar disorder.[3 4] However, the pathophysiological mechanisms for MMF are not clear.

A growing number of neuroimaging studies suggest that patients with MDD have dysfunction in the resting-state brain functional networks, especially the default mode network (DMN).[5–7] The DMN is a prominent intrinsic connectivity network, relating to consciousness, self-reference, social inference and autobiographical memory.[8] The DMN contains three subsystems: (1) the midline core subsystem, comprising the posterior

INTRODUCTION

Major depressive episode with mixed features (MMF) is a type of mood disorder that is often related to the switch of antidepressants or a

cingulate cortex (PCC) and anterior medial prefrontal cortex, relates to self-relevant and affective decisions; (2) the dorsal medial prefrontal cortex (dMPFC) subsystem, including the dMPFC, temporo-parietal junction, lateral temporal cortex and temporal pole, contributes to mentalizing and conceptual processing; and (3) the medial temporal lobe (MTL) subsystem, containing the ventral medial prefrontal cortex, posterior inferior parietal lobule, retrosplenial cortex, parahippocampal cortex and hippocampal formation, is associated with autobiographical memory.[9]

Several studies found increased connectivity within the DMN among patients with MDD. For example, an early meta-analysis of resting-state functional connectivity found that increased connectivity within the DMN of patients with MDD[5]. One study found the MDD patients exhibited increased connectivity within the dMPFC subsystem and between the dMPFC and MTL subsystems.[10] A more recent study found increased connectivity within the DMN core subsystem among older adults with MDD.[11] On the other hand, many studies found decreased connectivity within the DMN among patients with MDD. One study with a large sample found decreased connectivity within the DMN in recurrent MDD,[12] and a recent meta-analysis of the functional connectivity of the DMN subsystems found slightly decreased functional connectivity within the DMN core subsystem.[13] Moreover, a study investigating the effect of antidepressants on the DMN subsystems found decreased connectivity within the DMN core subsystem and between the DMN core and dMPFC subsystems in adult patients with MDD at baseline.[14] Despite the inconsistent findings, these results indicate that the DMN could play an important role in the physiopathology of MDD.

The task-based functional neuroimaging studies found that MDD patients comorbid with manic symptoms exhibited higher activation in the parietal, temporal and frontal regions during emotional inhibition condition versus non-emotional condition,[15] and the high levels of subthreshold manic symptoms were correlated with the higher right amygdala activity to happy faces.[16] However, very few studies have examined the resting-state functional connectivity in patients with MMF. Thus, it remains unclear whether the resting-state functional connectivity patterns of the DMN subsystems change in patients with MMF.

Based on the previous findings of DMN subsystems in the MDD, we hypothesised that patients with MMF might have abnormal connectivity within the DMN subsystems. Therefore, this study aimed to investigate the functional connectivity of subsystems within the DMN of patients with MMF.

METHODS
Study design and participants
This is a cross-sectional study. A total of 74 patients were recruited from the outpatient department of Beijing Anding Hospital, Capital Medical University, between April 2021 and June 2022. Among them, 47 were patients with MDD without mixed features (MDD_{noMF}) and 27 were patients with MMF. All patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) by two experienced psychiatrists. The patients who were diagnosed with MDD and had fewer than two manic/hypomanic symptoms were considered as patients with MDD_{noMF}. The patients who met the full diagnostic criteria for MDD and had at least three manic/hypomanic features (eg, an excessively elevated mood, inflated self-esteem or grandiosity, more talkative than usual or feeling pressured to keep talking, flight of ideas or racing thoughts, increase in energy or goal-directed activity, increased or excessive involvement in activities that have a high potential for painful consequences, and decreased need for sleep) during the majority of days of the current or recent major depressive episode were diagnosed as patients with MMF.[17] All patients were right-handed and 18–55 years of age. The patients were excluded if they had any co-existing or history of other psychiatric disorders, such as schizophrenia or bipolar disorder, any major medical illnesses, a clinical diagnosis of neurological trauma, any history of substance or alcohol abuse, and any contraindications to magnetic resonance imaging (MRI) scanning. A total of 45 age- and gender-matched healthy controls (HCs) were recruited through advertisements by the Beijing Anding Hospital, Capital Medical University. The study flowchart is presented in figure 1.

Clinical assessment
The sociodemographic data and clinical characteristics were collected by the use of a predesigned data collection
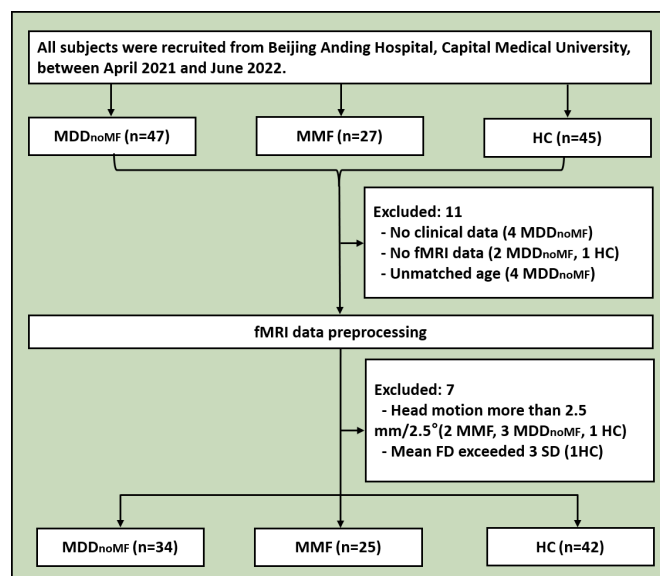
Figure 1 Flowchart of enrolment of the subjects. fMRI, functional MRI; FD, frame-wise displacement; HC, healthy control; MDD_{noMF}, major depressive disorder without mixed features; MMF, major depressive episode with mixed features; SD, standard deviation.

form. The severity of MDD was assessed with the 17-item Hamilton Depression Rating Scale (HAMD-17).[18] The manic/hypomanic symptoms were measured using the Young Mania Rating Scale (YMRS).[19]

Data acquisition
All the subjects underwent resting-state functional MRI (fMRI) scanning using a Siemens Prisma 3.0 T MRI scanner with a 64-channel phased-array head coil. The structural images were acquired using the T1-weighted magnetization-prepared rapidly acquired gradient-echo sequence with the following parameters: repetition time (TR)=2530 ms; flip angle (FA)=15°; echo time (TE)=1.85 ms; matrix=256×256; field of view (FOV)=256×256 mm^2; number of slices=192; slice thickness=1 mm; voxel size=1×1×1 mm^3. The resting-state fMRI images were acquired using a gradient-recall echo-planar imaging pulse sequence with the following parameters: TR=2000 ms; TE=30 ms; FA=90°; matrix=64×64; FOV=200×200 mm^2; number of slices=33; slice thickness=3.5 mm; gap=0.7 mm; voxel size=3.13×3.13×4.2 mm^3; phase encoding direction=anterior to posterior; 200 volumes. During the scanning, the subjects were required to keep their eyes closed, remain awake, relax their minds and keep still without any head motion.

Data preprocessing
Data preprocessing was carried out using Data Processing & Analysis for (Resting-State) Brain Imaging (V.6.0_210501, http://rfmri.org/DPABI). The first five time points were removed to ensure signal stability, and slice timing correction was performed. After the realignment, the T1 images were co-registered to the functional image. Afterwards, linear and quadratic trends, the first five principal c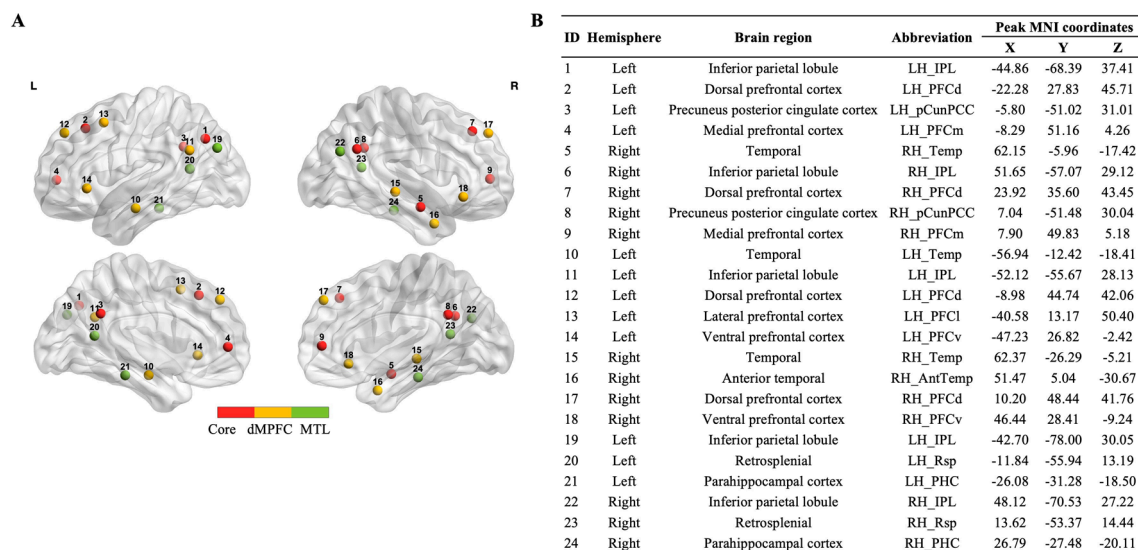omponents of the individually segmented white matter and cerebrospinal fluid, and Friston's 24 motion parameters were regressed out as covariates. The images were then normalized to the Montreal Neurological Institute template, and each voxel was resampled to 2×2×2 mm^3. Spatial smoothing was conducted using a Gaussian kernel with a full width half-maximum of 4 mm, and band-pass temporal filtering was performed at a range of 0.01–0.1 Hz. To quantify microhead motions, the 'bad' time points were removed from the time series by employing a 'scrubbing' method with a frame-wise displacement (FD)[20] threshold of 0.5 mm. The subjects whose head motion was >2.5 mm maximum translation in any direction of x, y or z or 2.5° of maximum rotation or if their mean FD exceeded 3 SD of the mean value were excluded.[21]

Definition of ROIs
A total of 24 regions of interest (ROI) were extracted from the 17-network parcellation by Yeo et al.[22] They were divided into three DMN subsystems: nine ROIs belong to the core subsystem, nine ROIs belong to the dMPFC subsystem and six ROIs belong to the MTL subsystem (figure 2).

Functional connectivity analyses
First, seed-based functional connectivity analyses were conducted to calculate the functional connectivities among ROIs in the three DMN subsystems. We extracted mean time series from each ROI, calculated Pearson's correlations between each pair of ROIs and applied Fisher's R-to-Z transformation, forming a 24×24 functional connectivity matrix for each subject. Second, the intranetwork functional connectivity in the three DMN subsystems was individually calculated with the averaged functional connectivity of ROIs within each of the DMN

ID	Hemisphere	Brain region	Abbreviation	Peak MNI coordinates		
				X	Y	Z
1	Left	Inferior parietal lobule	LH_IPL	-44.86	-68.39	37.41
2	Left	Dorsal prefrontal cortex	LH_PFCd	-22.28	27.83	45.71
3	Left	Precuneus posterior cingulate cortex	LH_pCunPCC	-5.80	-51.02	31.01
4	Left	Medial prefrontal cortex	LH_PFCm	-8.29	51.16	4.26
5	Right	Temporal	RH_Temp	62.15	-5.96	-17.42
6	Right	Inferior parietal lobule	RH_IPL	51.65	-57.07	29.12
7	Right	Dorsal prefrontal cortex	RH_PFCd	23.92	35.60	43.45
8	Right	Precuneus posterior cingulate cortex	RH_pCunPCC	7.04	-51.48	30.04
9	Right	Medial prefrontal cortex	RH_PFCm	7.90	49.83	5.18
10	Left	Temporal	LH_Temp	-56.94	-12.42	-18.41
11	Left	Inferior parietal lobule	LH_IPL	-52.12	-55.67	28.13
12	Left	Dorsal prefrontal cortex	LH_PFCd	-8.98	44.74	42.06
13	Left	Lateral prefrontal cortex	LH_PFCl	-40.58	13.17	50.40
14	Left	Ventral prefrontal cortex	LH_PFCv	-47.23	26.82	-2.42
15	Right	Temporal	RH_Temp	62.37	-26.29	-5.21
16	Right	Anterior temporal	RH_AntTemp	51.47	5.04	-30.67
17	Right	Dorsal prefrontal cortex	RH_PFCd	10.20	48.44	41.76
18	Right	Ventral prefrontal cortex	RH_PFCv	46.44	28.41	-9.24
19	Left	Inferior parietal lobule	LH_IPL	-42.70	-78.00	30.05
20	Left	Retrosplenial	LH_Rsp	-11.84	-55.94	13.19
21	Left	Parahippocampal cortex	LH_PHC	-26.08	-31.28	-18.50
22	Right	Inferior parietal lobule	RH_IPL	48.12	-70.53	27.22
23	Right	Retrosplenial	RH_Rsp	13.62	-53.37	14.44
24	Right	Parahippocampal cortex	RH_PHC	26.79	-27.48	-20.11

Figure 2 Regions of interest in default mode network (DMN). (A) Distributions of the three subsystems of the DMN. The red nodes represent the regions in the DMN core subsystem; the yellow nodes represent the regions in the DMN dorsal medial prefrontal cortex (dMPFC) subsystem, and the green nodes represent the regions in the DMN medial temporal lobe (MTL) subsystem. (B) The coordinates of the regions of interest (ROI) of the DMN subsystems. L, left; MNI, Montreal Neurological Institute; R, right.

subsystems. The internetwork functional connectivity was calculated with the mean of pairwise connections between the DMN subsystems. The edge functional connectivity within each of the DMN subsystems was the connectivity between pairs of ROIs within this subsystems.

Statistical analysis

Data were analysed using SPSS software, V.24.0 and R, V.4.2.1. The comparisons of sociodemographic and clinical characteristics between MDD_{noMF}, MMF and HC were performed using χ^2 tests, one-way analysis of variance (ANOVA) or Kruskal-Wallis H test, as appropriate. The significance level was set as 0.05 (two-tailed).

Analysis of covariance (ANCOVA) was conducted to compare the differences of the intranetwork and internetwork functional connectivity in the DMN subsystems among the MDD_{noMF}, MMF and HC groups, controlling for age, gender and mean FD. In addition, the edge connectivity within the abnormal DMN subsystems was further compared using the ANCOVA method. The false discovery rate (FDR) was used for multiple comparisons, and the FDR-adjusted p values <0.05 were considered statistically significant. The post hoc least significant difference analyses were applied for multiple group comparisons. The correlations between the abnormal intranetwork functional connectivity of the DMN subsystems and the total score of clinical scales were calculated for the patients using Pearson's correlation, or Spearman's correlation method, as appropriate.

RESULTS
Demographic and clinical characteristics comparisons

After excluding some subjects (for details, please see figure 1), a total of 34 patients with MDD_{noMF}, 25 patients with MMF and 42 HCs were included in the study. The demographic and clinical characteristics are summarised in table 1. The age, sex and mean FD were not significantly different among the groups (all p-values>0.05). There were significant differences in the education level and the total scores of the HAMD-17 and YMRS scales among the three groups. Compared with HC group, the patients with MDD_{noMF} and MMF had higher education levels. The patients with MDD_{noMF} and MMF had significantly higher HAMD-17 scores than the HCs, while no significant difference existed between the patients with MDD_{noMF} and MMF. The patients with MMF had higher YMRS scores than those with MDD_{noMF} and the HCs.

Differences in functional connectivity of the DMN subsystems

The intranetwork functional connectivity of the DMN core subsystem (F=6.32, p_{FDR}=0.008) and the MTL subsystem (F=4.45, p_{FDR}=0.021) showed significant differences among the MDD_{noMF}, MMF and HC groups. No significant differences were found in the intranetwork functional connectivity of the DMN dMPFC subsystem and in the internetwork functional connectivities between the DMN subsystems.

As shown in figure 3, compared with HCs, the patients with MDD_{noMF} and MMF showed increased functional connectivity within the DMN MTL subsystem (mean difference (HC–MDD_{noMF})=−0.11, SE=0.04, p=0.008, 95% CI: −0.19 to −0.03; mean difference (HC–MMF)=−0.10, SE=0.04, p=0.029, 95% CI: −0.18 to −0.01). Meanwhile, the MMF had increased functional connectivity within the DMN core subsystem (mean difference (HC–MMF)=−0.14, SE=0.04, p=0.001, 95% CI: −0.22 to −0.06). In addition, the patients with MMF also had increased functional connectivity within the DMN core subsystem compared with patients with MDD_{noMF} (mean difference

Table 1 Demographic and clinical characteristics

	HC N=42	MDD_{noMF} N=34	MMF N=25	H/χ^2	P value
Age (mean (SD))	26.55 (7.61)	28.26 (5.25)	28.32 (7.47)	5.07	0.079*
Male (n (%))	15 (35.71)	9 (26.47)	8 (32.00)	0.74	0.690†
Education (n, %)				25.07	<0.001†
Elementary	7 (16.67)	0 (0)	2 (8.00)		
Secondary	16 (38.10)	3 (8.82)	1 (4.00)		
Tertiary	19 (45.24)	31 (91.18)	22 (88.00)		
Smoking (n (%))	8 (19.05)	4 (11.76)	6 (24.00)	1.55	0.462†
Drinking (n (%))	2 (4.76)	4 (11.76)	1 (4.00)	1.87	0.392†
Days medicated (mean (SD))	0 (0)	67 (125)	60 (99)	60.67	<0.001*
Mean FD (mean (SD))	0.13 (0.06)	0.12 (0.05)	0.14 (0.07)	2.60	0.273*
HAMD-17 (mean (SD))	0.71 (1.20)	14.29 (5.45)	15.75 (7.12)	69.90	<0.001*
YMRS (mean (SD))	0.00 (0.00)	1.03 (2.44)	4.42 (2.84)	24.86	<0.001*

*Kruskal-Wallis H test.
†χ^2 tests.
FD, frame-wise displacement; HAMD-17, 17-item Hamilton Depression Rating Scale; HC, healthy control; MDD_{noMF} major depressive disorder without mixed features; MMF, major depressive episode with mixed features; SD, standard deviation; YMRS, Young Mania Rating Scale.
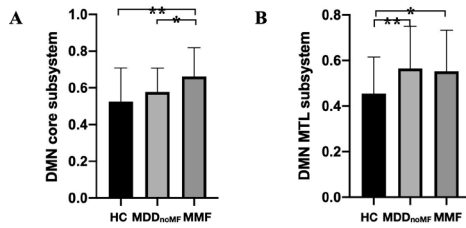
Figure 3 The significant difference of the intrasubsystem connectivity among the MDD_{noMF}, MMF and HC groups. (A) The connectivity within the DMN core subsystem; (B) the connectivity within the DMN MTL subsystem. DMN, default mode network; HC, healthy control; MDD_{noMF}, major depressive disorder without mixed features; MMF, major depressive disorder with mixed features; MTL, medial temporal lobe. *p<0.05; **p<0.01.

(MDD_{noMF}–MMF)=−0.08, SE=0.04, p=0.048, 95% CI: −0.17 to −0.001).

Furthermore, we compared the edge functional connectivity within the abnormal DMN subsystems among the MDD_{noMF}, MMF and HC groups. We found there was a range of abnormal edge connections in the DMN core subsystem, whereas no significant abnormal edge connections existed in the DMN MTL subsystem. In the DMN core subsystem, the edge connectivity of the LH_IPL–LH_PFCm (F=6.85, p_{FDR}=0.016), LH_IPL–RH_PFCm (F=7.59, p_{FDR}=0.016), LH_PFCd–RH_PFCd (F=5.41, p_{FDR}=0.036), LH_PFCd–RH_PFCm (F=6.75, p_{FDR}=0.016), LH_pCunPCC–RH_PFCm (F=5.21, p_{FDR}=0.037), LH_PFCm–RH_pCunPCC (F=4.77, p_{FDR}=0.048), RH_PFCd–RH_PFCm (F=6.49, p_{FDR}=0.016), RH_pCunPCC–RH_PFCm (F=7.57, p_{FDR}=0.016) showed significant differences among the MDD_{noMF}, MMF and HC groups. Except for the functional connectivity of LH_pCunPCC–RH_PFCm, all these edge

connections were significantly increased in the patients with MMF compared with the HC group and the patients with MDD_{noMF} (figure 4).

Correlation analysis
The intranetwork functional connectivity in the DMN core or MTL subsystems was not significantly correlated with HAMD-17 or YMRS total scores among the patients with MDD_{noMF} and MMF.

DISCUSSION
Main findings
This study investigated the functional connectivity of the DMN subsystems in patients with MDD_{noMF} and MMF. Results revealed the patients with MMF showed significantly increased connectivity within the DMN core subsystem when compared with patients with MDD_{noMF}, and they have a wide spread of abnormal edge functional connectivity within the DMN core subsystem. These findings indicate the brain regions within the DMN core subsystems (eg, IPL, PFCm, PFCd and pCunPCC) might play a critical role in the pathological mechanisms underlying MMF. Meanwhile, the MMF also showed increased connectivity within the DMN MTL subsystem compared with the MDD_{noMF} and HC groups.

This study found significantly increased connectivity within the DMN core subsystem in patients with MMF and MDD_{noMF}, with higher connectivity in patients with MMF as compared to patients with MDD_{noMF}. The DMN core subsystem is associated with personally significant affective information, acting as a network hub, linking social and mnemonic processes of the dMPFC and MTL subsystems.[9 13 23] Lines of evidence reported increased
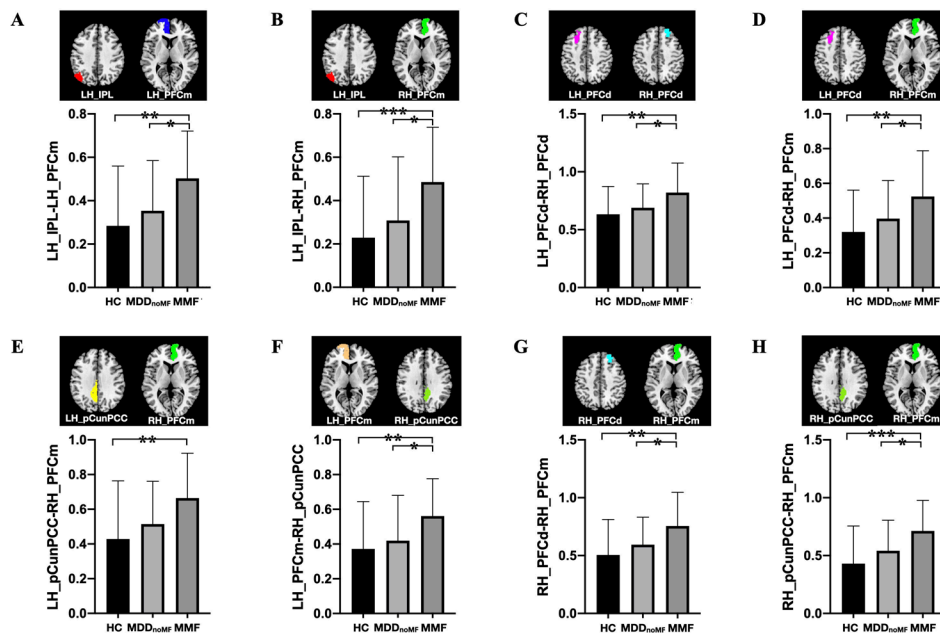
Figure 4 The significant differences in the functional connectivities between ROIs within the DMN core subsystems in the MDD_{noMF}, MMF and HC groups. HC, healthy control; MDD_{noMF}, major depressive disorder without mixed features; MMF, major depressive disorder with mixed features. *P<0.05; **P<0.01; ***P<0.001.

DMN connectivity in patients with MDD, which may be associated with a predominance of internalised, self-focused mental activity over efficient externally focused, and non-self-related attention.[5] [10] Abnormal connectivity of the DMN might lead to excessive focusing on external content and psychomotor overexcitement that can manifest in manic symptoms.[24] [25] The results of this study indicated that the increased connectivity of the DMN core in MMF could be a possible mechanism for the emotional disturbances that are experienced during major depressive episodes accompanying a manic episode.

In addition, our seed-based functional connectivity showed widespread increased edge connectivity within the DMN core subsystem in the patients with MMF compared with HC and patients with MDD$_{noMF}$. The mPFC, PCC and pCunPCC are considered as core hubs of the DMN.[24] [26] [27] These regions are central to emotional regulation and self-reference and executive functions–all areas where deficits have been reported in MDD.[28] Consistent with previous studies, the patients with MDD$_{noMF}$ showed increased functional connectivity in these regions compared with HCs.[29] [30] Moreover, patients with MMF displayed higher functional connectivity than the MDD$_{noMF}$ group, indicating MMF might be associated with worse emotional regulation skills. Considering the manic/hypomanic symptoms in the MMF, we inferred that increased functional connectivity in these regions could undermine emotional regulation, and may lead to the manic/hypomanic symptoms. As such, our findings raise an intriguing question: Could the connectivity between the regions within the core DMN subsystem be of importance for understanding the increased self-focus in depression and its relationship to difficulties with engaging in emotional regulation among patients with MMF.

Finally, increased connectivity within the MTL subsystem was found in the patients with MMF compared with the HC group; however, there was no significant difference when compared with the patients with MDD$_{noMF}$. The MTL is associated with autobiographical memory, episodic future thinking, information retrieval and imagery and navigation.[23] [31] The functional connectivity of the MTL subsystem is related to the frequency of thinking about the future.[32] Previous studies indicated that the patients with depressive symptoms have a lesser cognitive impairment than the patients with manic symptoms.[33] As noted, bipolar disorder patients have functional changes in brain regions related to autobiographical memory retrieval.[34] Hence, our findings suggest that abnormal connectivity within the MTL subsystem may imply a dysfunctional encoding of episodic memory in patients with MMF, but this may not be specific because the patients with MDD$_{noMF}$ also showed abnormality in this subsystem.

Limitations

Several limitations of this study should be taken into account. First, the sample size is relatively small. In future studies, we will expand the sample size to improve the reliability of findings. Second, some of the patients were taking antidepressant drugs, which might influence brain function. Future studies with first episodic, drug-naïve patients are encouraged. Third, this study applied a priori ROIs based on the brain altas. However, defining DMN by utilizing individual level approaches also needs to be explored in the future, such as the cortical parcellation approach,[35] and the machine learning algorithms.[36]

Implications

There are meaningful clinical implications from our findings. Our findings support the association between abnormal connectivity of the DMN subsystems with depression, and provide deeper insight into the pathophysiology associated with mixed features and depression symptoms. A related key finding of the study showed the patients with MMF presented abnormal functional connectivity within the DMN core subsystem, which might help deepen the understanding of the emotion regulation of the MMF. Furthermore, this insight may have key implications for the development and refinement of therapeutic interventions and diagnosis for patients with MMF.

CONCLUSION

In conclusion, this study investigated the functional connectivity in the DMN subsystems in patients with MDD$_{noMF}$ and MMF. Relative to patients with MDD$_{noMF}$, the MMF group displayed abnormal connectivity within the DMN core subsystem. Moreover, the patients with MMF also showed increased functional connectivity within the DMN MTL subsystem. These results indicate that the disrupted DMN subsystems might be associated with the pathophysiology of MMF. Functional connectivity in the DMN core subsystem might have the potential as a biomarker to diagnose the mixed features of patients with MDD.

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