



OPEN ACCESS

EDITED BY

Zhiyong Zhao,
Zhejiang University, China

REVIEWED BY

Chao Li,
The First Affiliated Hospital of China Medical
University, China
Lanxin Ji,
New York University, United States
Zhengyuan Yang,
University of Macau, China

*CORRESPONDENCE

Yao Zhu
✉ Yaoz88@outlook.com
Xuzhou Li
✉ lixuzhou@ynnu.edu.cn;
✉ xuzhouli_ecnupsy@126.com

[†]These authors have contributed equally to this work

RECEIVED 06 October 2023

ACCEPTED 24 November 2023

PUBLISHED 11 December 2023

CITATION

Zhu Y, Huang T, Li R, Yang Q, Zhao C, Yang M, Lin B, the DIRECT Consortium and Li X (2023) Distinct resting-state effective connectivity of large-scale networks in first-episode and recurrent major depression disorder: evidence from the REST-meta-MDD consortium. *Front. Neurosci.* 17:1308551. doi: 10.3389/fnins.2023.1308551

COPYRIGHT

© 2023 Zhu, Huang, Li, Yang, Zhao, Yang, Lin, the DIRECT Consortium and Li. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Distinct resting-state effective connectivity of large-scale networks in first-episode and recurrent major depression disorder: evidence from the REST-meta-MDD consortium

Yao Zhu^{1*†}, Tianming Huang^{2†}, Ruolin Li³, Qianrong Yang⁴, Chaoyue Zhao¹, Ming Yang¹, Bin Lin⁵, the DIRECT Consortium and Xuzhou Li^{4*}

¹School of Psychology and Cognitive Science, East China Normal University, Shanghai, China,

²Department of General Psychiatry, Shanghai Changning Mental Health Center, Shanghai, China,

³Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA, United States, ⁴Faculty of Education, Yunnan Normal University, Kunming, Yunnan, China, ⁵Department of Radiology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Introduction: Previous studies have shown disrupted effective connectivity in the large-scale brain networks of individuals with major depressive disorder (MDD). However, it is unclear whether these changes differ between first-episode drug-naïve MDD (FEDN-MDD) and recurrent MDD (R-MDD).

Methods: This study utilized resting-state fMRI data from 17 sites in the Chinese REST-meta-MDD project, consisting of 839 patients with MDD and 788 normal controls (NCs). All data was preprocessed using a standardized protocol. Then, we performed a granger causality analysis to calculate the effectivity connectivity (EC) within and between brain networks for each participant, and compared the differences between the groups.

Results: Our findings revealed that R-MDD exhibited increased EC in the fronto-parietal network (FPN) and decreased EC in the cerebellum network, while FEDN-MDD demonstrated increased EC from the sensorimotor network (SMN) to the FPN compared with the NCs. Importantly, the two MDD subgroups displayed significant differences in EC within the FPN and between the SMN and visual network. Moreover, the EC from the cingulo-opercular network to the SMN showed a significant negative correlation with the Hamilton Rating Scale for Depression (HAM-D) score in the FEDN-MDD group.

Conclusion: These findings suggest that first-episode and recurrent MDD have distinct effects on the effective connectivity in large-scale brain networks, which could be potential neural mechanisms underlying their different clinical manifestations.

KEYWORDS

major depressive disorder, first-episode and recurrent, resting-state fMRI, brain networks, effective connectivity

Introduction

Major depressive disorder (MDD) is a prevalent and debilitating psychiatric disorder that affects 4.7% of the global population and is the second leading cause of disability worldwide (Ferrari et al., 2013). Neuroimaging studies have made significant efforts to explore the pathology underlying MDD. Abnormal functional connectivity (FC) within and between large-scale intrinsic brain networks (Yan et al., 2019; Liu et al., 2021; Sun et al., 2022a,b), such as the default mode network (DMN), executive control network (ECN), and salience network (SN), has been found in MDD using resting-state functional magnetic resonance imaging (rs-fMRI). This reflects that the synchronized spontaneous activity among anatomically distinct networks is potentially linked to rumination dysfunction (Hamilton et al., 2015), cognitive impairment (Clark et al., 2009), and emotional dysregulation (Zhao et al., 2021) in patients with MDD. However, inconsistencies in the FC of several networks like DMN, including increases, decreases, both increases and decreases, and no significant changes, have been reported in prior studies of brain networks in MDD (Yan et al., 2019). This may be related to low sensitivity and reliability, as well as limited statistical power due to small sample sizes (Button et al., 2013; Chen et al., 2018), leading to the pathophysiology of MDD remaining unknown.

According to the ICD-10, MDD can be classified as first-episode or recurrent depression (Hiller et al., 1994). The risk of relapse in MDD is directly proportional to the number of episodes (de Jonge et al., 2018). Compared to first-episode MDD, recurrent MDD exhibits more severe depressive and somatic symptoms, greater impairments in verbal memory, executive function, and mental representation processing (Roca et al., 2011; Nigatu et al., 2015), as well as higher medical costs (Kamlet et al., 1995; Biesheuvel-Leliefeld et al., 2012). Therefore, distinguishing the neuropathological mechanisms of first-episode and recurrent MDD is important for developing new and effective treatment protocols. A prior large-sample study found FC reduction of DMN in recurrent but not in first-episode MDD, which was associated with duration of illness rather than medication usage, suggesting this alteration is related to symptom severity (Yan et al., 2019). Another study revealed that compared with healthy controls, both first-episode and recurrent MDD showed reduced FC in the DMN and affective network, whereas the decrease in cognitive control network only occurred in first-episode MDD (Sun et al., 2022a,b). Compared with recurrent MDD, first-episode MDD showed hypoconnectivity in the DMN, dorsal attention network (DAN), and somatomotor network (Liu et al., 2021). However, these FC findings did not consider the direction of information communication between networks.

Effective connectivity (EC) represents the direct or indirect causal effect of one brain region on another (Deshpande et al., 2011; Deshpande and Xiaoping, 2012). In EC methods, Granger causality analysis (GCA) is a relatively data-driven analytical method that does not require the design of a complicated task. It is more convenient for clinical application than model-driven Structural equation modeling (SEM) and Dynamic causal modeling (DCM) (Seminowicz et al., 2004; Schlösser et al., 2008). GCA analyzes the direction of information flow between brain areas using time series of information processing and can depict resting-state directional brain networks (Jiao et al., 2014). A prior study has demonstrated that the EC measure may play a more important role than FC in exploring alterations in

disease brains and afford better mechanistic interpretability (Geng et al., 2018). Studies on MDD have reported abnormal EC in several brain regions such as the amygdala (de Almeida et al., 2009), prefrontal cortex (Hamilton et al., 2011), and insula (Iwabuchi et al., 2014; Kandilarova et al., 2018), as well as in networks such as DMN, SN, and DAN (Guo et al., 2020; Li et al., 2020; Wang et al., 2022). However, the similarities and differences of EC between first-episode and recurrent MDD in large-scale networks have been less studied using GCA.

In this study, we obtained resting-state fMRI data from 839 patients with MDD and 788 matched normal controls (NCs) from the Chinese REST-meta-MDD project. We used GCA to explore alterations in the EC within and between brain networks in first-episode and recurrent MDD. We also estimated the correlation between EC and clinical assessments. Our hypothesis was that the two MDD subgroups would show different changes in intra- and inter-network EC.

Methods

Participants

We utilized rs-fMRI data from the REST-meta-MDD consortium (Chen et al., 2023), comprising 1,300 MDD patients and 1,128 NCs across 23 sites. Each participant underwent a T1-weighted structural scan and an rs-fMRI scan. The patient inclusion criteria, as reported in the study (Yan et al., 2019), were as follows: (1) 18 years < age < 65 years; (2) education > 5 years; (3) fulfillment of the Diagnostic and Statistical Manual of Mental Disorders-IV criteria for MDD; and (4) a total score of ≥ 8 on the 17-item Hamilton Depression Rating Scale (HAM-D) at the time of scanning. The exclusion criteria included: (1) any contraindications for undergoing MRI; (2) poor spatial normalization, coverage, or excessive head motion; (3) incomplete information; and (4) sites with fewer than 10 patients in either group. Consequently, we obtained data from 839 MDD patients and 788 NCs across 17 sites. In terms of subgroups, we compared 227 first-episode drug-naïve (FEDN) patients with 388 matched NCs from five sites, 189 recurrent MDD patients with 423 matched NCs from six sites, and 117 FEDN patients with 72 recurrent MDD patients from two sites. The HAM-D and Hamilton Anxiety Rating Scale (HAMA) were employed to assess depression and anxiety symptoms in each patient, respectively.

All data were identified and anonymized. Local Institutional Review Boards approved all contributing studies, and participants signed a written informed consent at each local institution.

fMRI preprocessing

All rs-fMRI scans were preprocessed at each site utilizing the identical DPARSF protocol as reported in Yan et al. (2019). Specifically, the initial 10 volumes were discarded and slice-timing correction was performed. Subsequently, a rigid body transformation was used to realign the time series of images for each subject. After that, individual T1-weighted images were co-registered to the mean functional image using a 6 degrees-of-freedom linear transformation without re-sampling, and then segmented into gray matter (GM),

white matter (WM), and cerebrospinal fluid (CSF). Following this, transformations from individual native space to MNI space were computed using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) tool (Ashburner, 2007) and applied to individual functional images. The Friston 24-parameter model, WM, and CSF signals were removed from normalized data through linear regression. Lastly, a linear trend was included as a regressor to account for drifts in the BOLD signal and temporal band-pass filtering (0.01–0.1 Hz) was applied to all time series.

Effective connectivity analysis

We used the DOS-160 atlas (Dosenbach et al., 2010) to segment the brain into 160 regions of interest (ROIs) involved in six networks: cingulo-opercular network (CON), FPN, DMN, sensorimotor network (SMN), visual network (VN), and cerebellum network (CN) (Figure 1). We extracted the averaged time series for each ROI and calculated the EC between any paired ROIs using the GCA method. Then, we computed intra- and inter-network EC by averaging the connectivities between ROIs belonging to the same or different networks, respectively, and the averaged EC with each ROI or network as a seed.

Statistical analysis

We employed a linear mixed model (LMM) (West et al., 2022) to compare differences in EC between MDD and NC, FEDN and NC, recurrent MDD and NC, and FEDN and recurrent MDD, respectively. The model was following: $y \sim 1 + \text{Diagnosis} + \text{Age} + \text{Sex} + \text{Education} + \text{Motion} + (1|\text{Site}) + (\text{Diagnosis}|\text{Site})$, in which y represents the EC value. This yields t and p values for the fixed effect of Diagnosis (Yan et al., 2019). To test relationships between EC and clinical assessments, we replaced the ‘ y ’ in the LMM with HAMD or HAMA scores, respectively. The multiple comparisons were corrected using false discovery rate (FDR) correction ($p < 0.05$).

Results

Characteristics of participants

As shown in Table 1, two MDD subgroups had no significant differences than NCs in age and gender ($p > 0.05$), but showed lower education than NCs ($p < 0.001$). Recurrent MDD showed a longer duration of illness than FEDN ($p < 0.001$). FEDN and recurrent MDD showed no significant differences in age, gender, and education ($p > 0.05$). Total MDD (mixture of FEDN and recurrent MDD) showed significant differences in education ($p < 0.001$) and gender ($p = 0.005$) but not age ($p > 0.05$) compared with NCs.

Between-group differences in EC of large-scale brain networks

As shown in Figures 2, 3, total MDD showed decreased afferent EC to the CN, increased efferent EC from the FPN, and increased EC from SMN to FPN compared with NCs. When MDD was divided into two subgroups, FEDN showed increased EC from SMN to FPN compared to NCs, and decreased EC from SMN to VN relative to recurrent MDD. Recurrent MDD showed stronger efferent EC in the ventral lateral prefrontal cortex (vlPFC) with all other regions in the whole brain relative to both NCs and FEDN, and decreased afferent to the CN and efferent EC from the SMN compared with NCs. The FEDN showed no significant difference in seed-based network EC compared to NCs, and the recurrent MDD showed no significant difference in inter-network EC compared to NCs.

Correlation

The EC from CON to SMN showed a significant negative correlation ($p = 0.004$, $R = -0.20$) with the HAMD score in the FEDN group (Figure 4). No significant correlations were observed in the total MDD and recurrent MDD groups. There was no significant correlations between EC and the HAMA score in all groups.

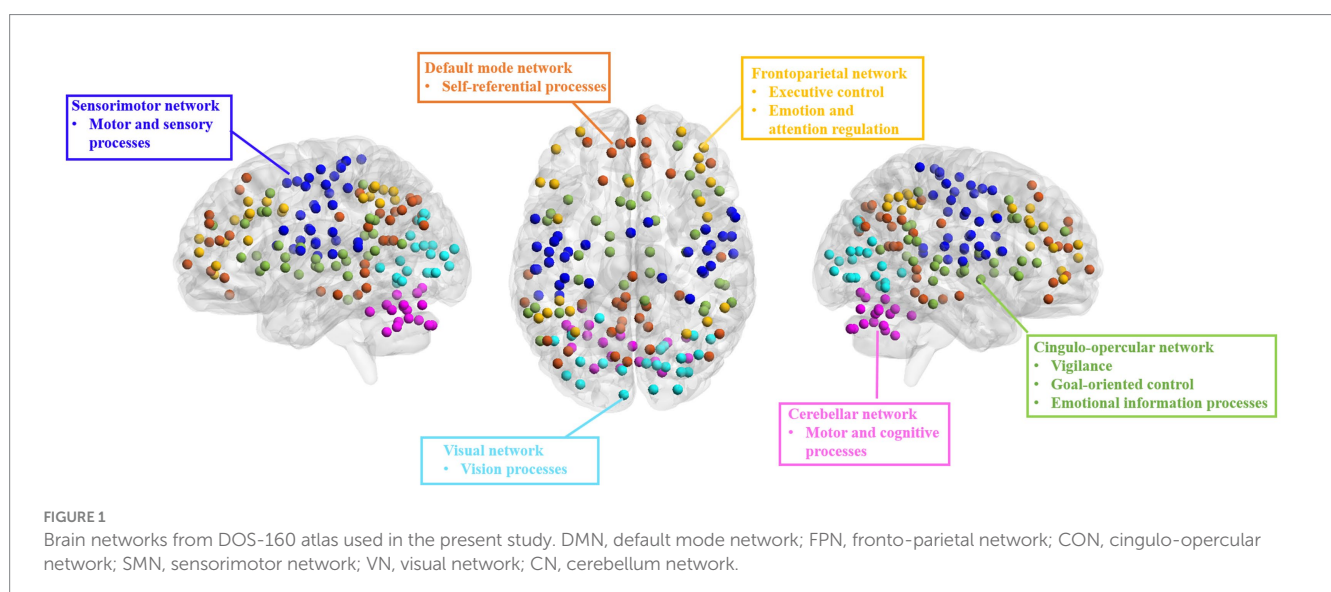


TABLE 1 Demographic characteristics of participants.

| | MDD vs NC | | | FEDN vs NC | | | RMDD vs NC | | | FEDN vs RMDD | | |
|------------------|---------------|--------------|---------|----------------|--------------|---------|----------------|--------------|---------|----------------|---------------|---------|
| | MDD (N = 848) | NC (N = 794) | p-value | FEDN (N = 232) | NC (N = 394) | p-value | RMDD (N = 189) | NC (N = 427) | p-value | FEDN (N = 119) | RMDD (N = 72) | p-value |
| Age | 34.3 ± 11.5 | 34.4 ± 13.0 | 0.313 | 32.7 ± 10.4 | 35.7 ± 14.2 | 0.154 | 35.4 ± 12.5 | 37.1 ± 14.1 | 0.333 | 35.4 ± 11.3 | 36.3 ± 12.7 | 0.865 |
| Sex (male, n%) | 474(36.5%) | 474(42.1%) | 0.005 | 78(33.6%) | 152(38.6%) | 0.214 | 78(41.3%) | 167(39.1%) | 0.613 | 40(33.6%) | 30(41.7%) | 0.263 |
| Education | 12.0 ± 3.4 | 13.6 ± 3.4 | <0.001 | 12.2 ± 3.4 | 13.6 ± 3.6 | <0.001 | 11.7 ± 3.2 | 13.4 ± 3.8 | <0.001 | 11.5 ± 3.4 | 12.0 ± 3.5 | 0.270 |
| Head Motion | 0.07 ± 0.04 | 0.07 ± 0.04 | 0.920 | 0.06 ± 0.03 | 0.07 ± 0.04 | 0.455 | 0.07 ± 0.04 | 0.07 ± 0.04 | 0.910 | 0.06 ± 0.03 | 0.07 ± 0.03 | 0.566 |
| Duration (month) | 38.4 ± 60.6 | NA | NA | 17.7 ± 30.8 | NA | NA | 92.7 ± 86.1 | NA | NA | 27.0 ± 39.5 | 88.7 ± 80.1 | <0.001 |
| Site | 17 | 17 | 1.000 | 5 | 5 | 1.000 | 6 | 6 | 1.000 | 2 | 2 | 1.000 |
| HAMD | 21.7 ± 6.6 | NA | NA | 22.5 ± 5.4 | NA | NA | 17.7 ± 7.8 | NA | NA | 22.1 ± 4.2 | 21.3 ± 5.8 | 0.371 |
| HAMA | 19.2 ± 8.9 | NA | NA | 21.9 ± 9.3 | NA | NA | 13.9 ± 10.5 | NA | NA | 11.2 ± 8.3 | 11.4 ± 10.5 | 0.342 |

Discussion

This study used GCA to explore alterations in EC within and between resting-state networks in FEDN and recurrent MDD patients in a large-sample Chinese population. We found that: (1) recurrent and total MDD showed altered EC in the FPN, SMN, and CN compared to NCs, while FEDN and total MDD showed altered inter-network EC from SMN to FPN compared to NCs; (2) two MDD subgroups showed significant differences in intra-network EC of the vIPFC within the FPN and in inter-network EC from SMN to VN; (3) the EC from CON to SMN showed a significant negative correlation with the HAMD score in FEDN but not in recurrent MDD group. These findings suggest that the EC among large-scale brain networks at rest was disrupted in patients with MDD, and that recurrent MDD exhibited different effective connections from FEDN.

The previous studies demonstrated that repetitive transcranial magnetic stimulation to the vIPFC reduced individual depersonalization symptoms (American Psychiatric Association, 2013; Jay et al., 2016). Increased activity in this region is linked with increased fronto-insula/limbic inhibitory regulation (Lemche et al., 2007) and may represent an increased effort to regulate emotions or be indicative of deficits in this area (Langenecker et al., 2007). Compared with healthy controls and MDD patients, bipolar disorder (BD) patients showed increased ventral prefrontal cortical responses to both positive and negative emotional expressions (Lawrence et al., 2004). A prior magnetic resonance spectroscopy study found that recurrent MDD showed more metabolite abnormalities in the ventral frontal cortex compared with both first-episode MDD and controls (Portella et al., 2011). A recent functional near-infrared spectroscopy study demonstrated different neurofunctional activity in frontal regions in FEDN and recurrent MDD, which linked between the level of complexity activation in these regions and cognitive impairment severity of patients (Yang et al., 2023). Another recent fMRI study reported that recurrent MDD had higher spontaneous brain activity in the prefrontal cortex compared to first-episode depression, which showed a positive correlation with depressive symptom severity (Sun et al., 2022a,b). Effective connectivity analysis revealed mutually propagating activation in ventral prefrontal cortex in people with MDD, which predicted higher levels of depressive rumination (Hamilton et al., 2011). Consistently, our study found that recurrent MDD had increased EC in the vIPFC compared with both FEDN and NCs, suggesting more severe depressive symptoms in recurrent patients, possibly associated with depersonalization, emotional regulation, and rumination.

Recent studies have demonstrated that the cerebellum plays a significant role in motor control, cognition, and emotion (Balasubramanian et al., 2021; Su et al., 2021). For example, Liu et al. (2012) found disrupted FC of the CN in adults with major depression, which could be associated with emotional disturbances and cognitive deficits. Liu et al. (2022) reported altered EC of the CN in patients with MDD, which was correlated with deficits in spatial-visual attention and psychomotor disorders. The FPN, also referred to as the executive network, plays a pivotal role in control function, execution, and emotion processing. It is strongly associated with cognitive problems in depression, especially those concerning executive functions. Dysfunctions within the FPN are likely connected to ineffective transmission of information between parietal and prefrontal regions (Brzezicka, 2013). Studies also reported alterations in FC strengths in

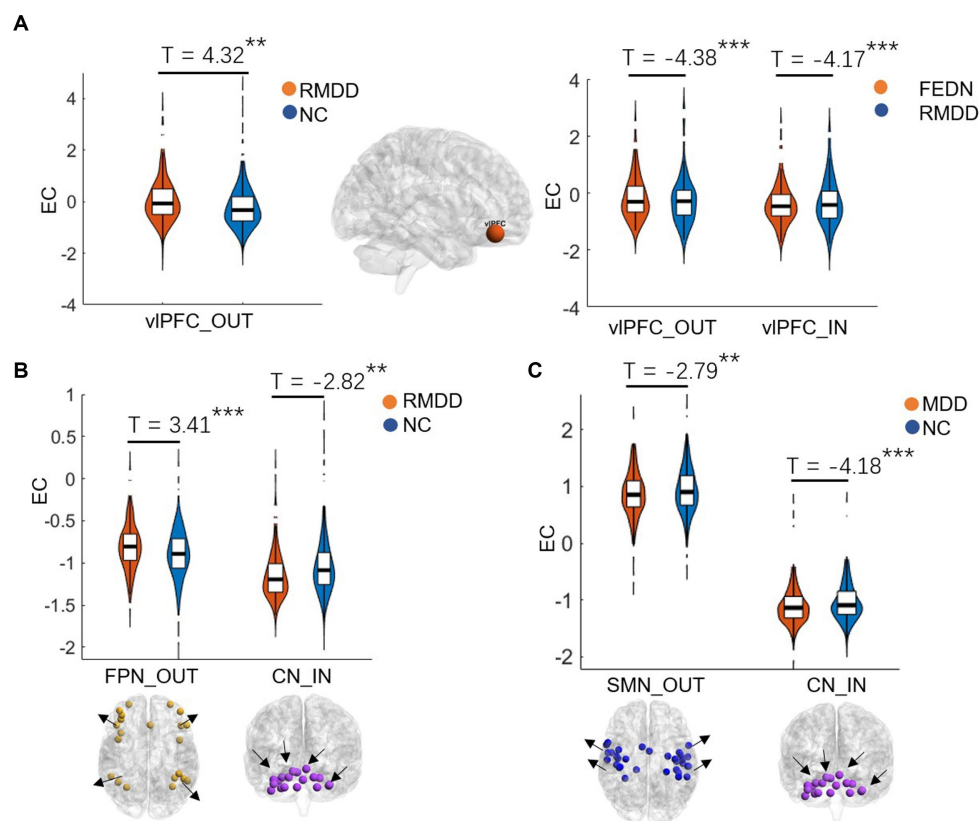


FIGURE 2 Differences between groups in effective connectivity of brain networks. FEDN, first-episode drug-naïve; RMDD, recurrent major depression disorder; vIPFC, ventral lateral prefrontal cortex; FPN, fronto-parietal network; SMN, sensorimotor network; CN, cerebellum network. ** $p < 0.05$; *** $p < 0.001$.

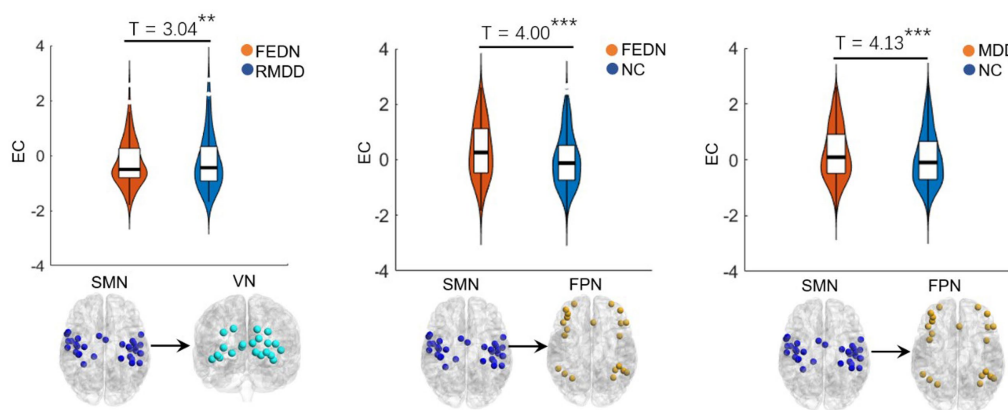
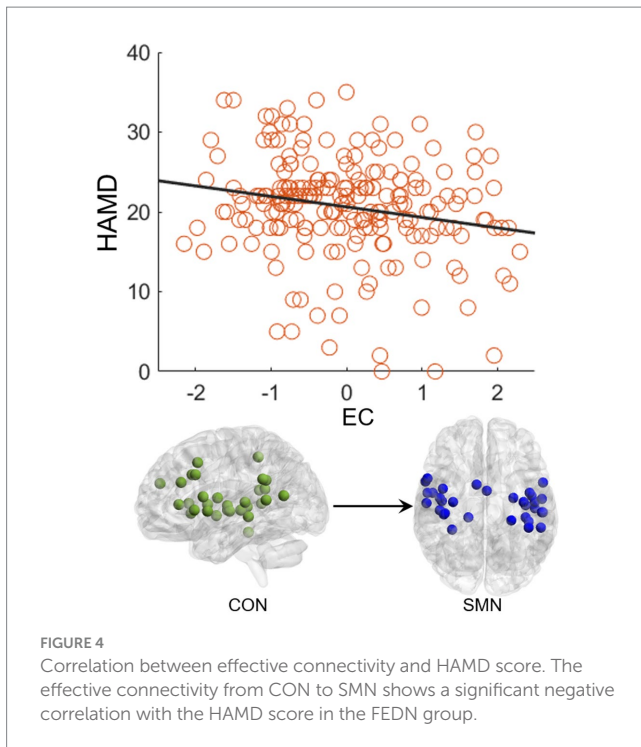


FIGURE 3 Inter-network differences in effective connectivity between groups. FEDN, first-episode drug-naïve; RMDD, recurrent major depression disorder; FPN, fronto-parietal network; SMN, sensorimotor network; VN, visual network. ** $p < 0.05$; *** $p < 0.001$.

the frontal and sensorimotor networks (Pang et al., 2020) and disrupted interhemispheric coordination in SMN in MDD patients (Zhang et al., 2023). Moreover, individuals with long-duration MDD showed increased FC in the FPN compared to those with short-duration MDD (Sheng et al., 2022). Similarly, the present study found altered EC of the FPN, CN, and SMN in total MDD and recurrent MDD but not in FEDN, which could be associated with functional

impairments of cognitive processing, perception and information integration (Lu et al., 2020), and treatment response-related changes in depression (Dichter et al., 2015). These findings may serve as a potentially effective biomarker for recurrent MDD.

Many studies have found significantly altered connections in low-order networks such as the SMN and VN in MDD patients (Wei et al., 2015; Sambataro et al., 2017). The sensorimotor



cortex is a brain region that has attracted much attention in depression research (Ray et al., 2021). Several sensorimotor interventions, including light, music, and physical exercise are known to modulate mood and depressive symptoms (Canbeyli, 2013). Depression gives rise to sensorimotor alterations such as psychomotor retardation or agitation and feelings of fatigue, which are part of the diagnostic criteria for depression (Guha, 2014). Previous studies have found alterations of FC and cerebral blood flow in the SMN related to psychomotor retardation in patients with depression (Yin et al., 2018; Yu et al., 2019), while task-based fMRI studies showed differential reactions of the visual cortex in depression (Rosa et al., 2015; Le et al., 2017). Lu et al. (2020) found reduced between-network FC in auditory and visual networks associated with depression. Kang et al. (2018) demonstrated abnormal primary somatosensory area-thalamic FC in MDD. Moreover, abnormal ECs among the FPN, VN, and SMN networks have been reported to be related to visual attention and cognitive behavior deficits in MDD patients (Kang et al., 2018). Therefore, the present study observed increased EC from SMN to FPN in both total MDD and FEDN compared to NCs, which may be compensation for sensory impairments, psychomotor retardation, and cognitive dysfunction of patients. In addition, a recent study uncovered that the ECs in sensorimotor cortices may serve as a promising and quantifiable candidate marker of depression severity and treatment response (Ray et al., 2021). Another study found that changes in information flow direction from SMN before and after electroconvulsive therapy were significantly correlated with improvement in depressive symptoms in MDD patients (Kyuragi et al., 2023). A small-sample study found that patients with recurrent MDD showed remarkably different effective connections compared to patients with first-episode MDD, especially related to the attention network (Wang et al., 2022).

Thus, the increased EC from the SMN to the VN in recurrent MDD relative to FEDN in the present study may be associated with depression severity and treatment of patients. Furthermore, the EC from CON to SMN negatively correlated with the HAMD score may serve as a biomarker to predict the severity of MDD.

Limitations

The present study has several limitations. First, the correlation analysis relied solely on HAMD scores of depression. There are a large number of rating scales for assessing depression severity, and each with its own advantages and limitations. Thus, the present neuroimaging findings could be further validated with a combination of observer rating scales and objective behavioral measures of depression (Lahnakoski et al., 2020). Second, we were unclear about the medication history of the recurrent MDD patients, and therefore the present findings are in need of replication. Third, MDD patients in the present study were the Chinese populations, which might not be generalized to other regions or populations. Fourth, the use of LMM should be discussed with regard to its potential limitations, such as its comparison to other methods or its applicability to this specific study. Finally, as a cross-sectional study, changes in connections with disease progression cannot be thoroughly reflected by the limited nodes. Further efforts, such as intervention studies with comparisons before and after medication, are required to draw valid conclusions on the impact of EC.

Conclusion

The present study used the GCA method to investigate differences in EC of large-scale brain networks in FEDN and recurrent MDD patients. We found that recurrent MDD showed altered EC in the FPN, SMN, and CN, while FEDN showed altered inter-network EC from SMN to FPN compared with NCs. Meanwhile, the ECs within FPN and from SMN to VN displayed significant differences between two MDD subgroups. Moreover, the EC from CON to SMN showed a significant negative correlation with HAMD scores in FEDN but not recurrent MDD group. These findings suggest that first-episode and recurrent MDD may have different effective connectivity patterns among large-scale brain networks, which may serve as potential biomarkers for diagnosing MDD.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: <http://rfmri.org/REST-meta-MDD>.

Author contributions

YZ: Writing – original draft, Methodology, Software, Writing – review & editing. TH: Methodology, Writing – original draft. RL: Writing – original draft, Writing – review & editing. QY: Writing

– original draft, Writing – review & editing. CZ: Writing – review & editing, Methodology, Software. MY: Writing – review & editing, Methodology, Software. BL: Writing – review & editing, Formal analysis. XL: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by Innovation Team Program in Philosophy and Social Science of Yunnan Province (Research on psychological adaptation and development of China's ethnic minority students in border areas).

References

- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (American psychiatric association Washington, DC).
- Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage* 38, 95–113. doi: 10.1016/j.neuroimage.2007.07.007
- Balasubramanian, M., Mulkern, R. V., Neil, J. J., Maier, S. E., and Polimeni, J. R. (2021). Probing in vivo cortical myeloarchitecture in humans via line-scan diffusion acquisitions at 7 T with 250–500 micron radial resolution. *Magn. Reson. Med.* 85, 390–403. doi: 10.1002/mrm.28419
- Biesheuvel-Liefeld, K. E. M., Kersten, S., van der Horst, H. E., van Schaik, A., Bockting, C. L. H., Bosmans, J. E., et al. (2012). Cost-effectiveness of nurse-led self-help for recurrent depression in the primary care setting: design of a pragmatic randomised controlled trial. *BMC Psychiatry* 12, 1–9. doi: 10.1186/1471-244X-12-59
- Brzezicka, A. (2013). Integrative deficits in depression and in negative mood states as a result of fronto-parietal network dysfunctions. *Acta Neurobiol. Exp.* 73, 313–325.
- Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., et al. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nat. Rev. Neurosci.* 14, 365–376. doi: 10.1038/nrn3475
- Canbeyli, R. (2013). Sensorimotor modulation of mood and depression: in search of an optimal mode of stimulation. *Front. Hum. Neurosci.* 7:428. doi: 10.3389/fnhum.2013.00428
- Chen, X., Bin, L., Wang, Y.-W., Li, X.-Y., Wang, Z.-H., Li, H.-X., et al. (2023). The complexity of functional connectivity profiles of the Subgenual anterior cingulate cortex and dorsal lateral prefrontal cortex in major depressive disorder: a DIRECT consortium study. *bioRxiv*. doi: 10.1101/2023.03.09.531726
- Chen, X., Bin, L., and Yan, C.-G. (2018). Reproducibility of R-fMRI metrics on the impact of different strategies for multiple comparison correction and sample sizes. *Hum. Brain Mapp.* 39, 300–318. doi: 10.1002/hbm.23843
- Clark, L., Chamberlain, S. R., and Sahakian, B. J. (2009). Neurocognitive mechanisms in depression: implications for treatment. *Annu. Rev. Neurosci.* 32, 57–74. doi: 10.1146/annurev.neuro.31.060407.125618
- de Almeida, J., Cardoso, R., Versace, A., Mechelli, A., Hassel, S., Quevedo, K., et al. (2009). Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. *Biol. Psychiatry* 66, 451–459. doi: 10.1016/j.biopsych.2009.03.024
- de Jonge, M., Bockting, C. L. H., van Oppen, P., Van, H. L., Peen, J., Kikkert, M. J., et al. (2018). The association between the number of previous episodes and modifiable vulnerability factors in remitted patients with recurrent depression. *PLoS One* 13:e0206495. doi: 10.1371/journal.pone.0206495
- Deshpande, G., Santhanam, P., and Xiaoping, H. (2011). Instantaneous and causal connectivity in resting state brain networks derived from functional MRI data. *NeuroImage* 54, 1043–1052. doi: 10.1016/j.neuroimage.2010.09.024
- Deshpande, G., and Xiaoping, H. (2012). Investigating effective brain connectivity from fMRI data: past findings and current issues with reference to granger causality analysis. *Brain Connect.* 2, 235–245. doi: 10.1089/brain.2012.0091
- Dichter, G. S., Gibbs, D., and Smoski, M. J. (2015). A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder. *J. Affect. Disord.* 172, 8–17. doi: 10.1016/j.jad.2014.09.028
- Dosenbach, N. U. F., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., et al. (2010). Prediction of individual brain maturity using fMRI. *Science* 329, 1358–1361. doi: 10.1126/science.1194144
- Ferrari, A. J., Charlson, F. J., Norman, R. E., Flaxman, A. D., Patten, S. B., Vos, T., et al. (2013). The epidemiological modelling of major depressive disorder: application for the

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.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

global burden of disease study 2010. *PLoS One* 8:e69637. doi: 10.1371/journal.pone.0069637

Geng, X., Junhai, X., Liu, B., and Shi, Y. (2018). Multivariate classification of major depressive disorder using the effective connectivity and functional connectivity. *Front. Neurosci.* 12:38. doi: 10.3389/fnins.2018.00038

Guha, Martin. (2014). *Diagnostic and statistical manual of mental disorders: DSM-5, Ref. Rev.*, American Psychiatric Publishing, Inc., Arlington, VA

Guo, M., Wang, T., Zhang, Z., Chen, N., Li, Y., Wang, Y., et al. (2020). Diagnosis of major depressive disorder using whole-brain effective connectivity networks derived from resting-state functional MRI. *J. Neural Eng.* 17:056038. doi: 10.1088/1741-2552/abb2c8

Hamilton, J. P., Chen, G., Thomason, M. E., Schwartz, M. E., and Gotlib, I. H. (2011). Investigating neural primacy in major depressive disorder: multivariate granger causality analysis of resting-state fMRI time-series data. *Mol. Psychiatry* 16, 763–772. doi: 10.1038/mp.2010.46

Hamilton, J. P., Farmer, M., Fogelman, P., and Gotlib, I. H. (2015). Depressive rumination, the default-mode network, and the dark matter of clinical neuroscience. *Biol. Psychiatry* 78, 224–230. doi: 10.1016/j.biopsych.2015.02.020

Hiller, W., Dichtl, G., Hecht, H., Hundt, W., Mombour, W., and von Zerssen, D. (1994). Evaluating the new ICD-10 categories of depressive episode and recurrent depressive disorder. *J. Affect. Disord.* 31, 49–60. doi: 10.1016/0165-0327(94)90126-0

Iwabuchi, S. J., Peng, D., Fang, Y., Jiang, K., Liddle, E. B., Liddle, P. F., et al. (2014). Alterations in effective connectivity anchored on the insula in major depressive disorder. *Eur. Neuropsychopharmacol.* 24, 1784–1792. doi: 10.1016/j.euroneuro.2014.08.005

Jay, E.-L., Nestler, S., Sierra, M., McClelland, J., Kekic, M., and David, A. S. (2016). Ventrolateral prefrontal cortex repetitive transcranial magnetic stimulation in the treatment of depersonalization disorder: a consecutive case series. *Psychiatry Res.* 240, 118–122. doi: 10.1016/j.psychres.2016.04.027

Jiao, Z.-Q., Zou, L., Cao, Y., Qian, N., and Ma, Z.-H. (2014). Effective connectivity analysis of fMRI data based on network motifs. *J. Supercomput.* 67, 806–819. doi: 10.1007/s11227-013-1010-z

Kamlet, M. S., Paul, N., Greenhouse, J., Kupfer, D., Frank, E., and Wade, M. (1995). Cost utility analysis of maintenance treatment for recurrent depression. *Control. Clin. Trials* 16, 17–40. doi: 10.1016/0197-2456(94)00020-4

Kandilarova, S., Stoyanov, D., Kostianev, S., and Specht, K. (2018). Altered resting state effective connectivity of anterior insula in depression. *Front. Psych.* 9:83. doi: 10.3389/fpsy.2018.00083

Kang, L., Zhang, A., Sun, N., Liu, P., Yang, C., Li, G., et al. (2018). Functional connectivity between the thalamus and the primary somatosensory cortex in major depressive disorder: a resting-state fMRI study. *BMC Psychiatry* 18, 1–8. doi: 10.1186/s12888-018-1913-6

Kyuragi, Y., Oishi, N., Yamasaki, S., Hazama, M., Miyata, J., Shibata, M., et al. (2023). Information flow and dynamic functional connectivity during electroconvulsive therapy in patients with depression. *J. Affect. Disord.* 328, 141–152. doi: 10.1016/j.jad.2023.02.060

Lahnakoski, J. M., Forbes, P. A. G., McCall, C., and Schilbach, L. (2020). Unobtrusive tracking of interpersonal orienting and distance predicts the subjective quality of social interactions. *R. Soc. Open Sci.* 7:191815. doi: 10.1098/rsos.191815

Langenecker, S. A., Kennedy, S. E., Guidotti, L. M., Briceno, E. M., Own, L. S., Hooven, T., et al. (2007). Frontal and limbic activation during inhibitory control predicts treatment response in major depressive disorder. *Biol. Psychiatry* 62, 1272–1280. doi: 10.1016/j.biopsych.2007.02.019

- Lawrence, N. S., Williams, A. M., Surguladze, S., Giampietro, V., Brammer, M. J., Andrew, C., et al. (2004). Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biol. Psychiatry* 55, 578–587. doi: 10.1016/j.biopsych.2003.11.017
- Le, T. M., Borghi, J. A., Kujawa, A. J., Klein, D. N., and Leung, H.-C. (2017). Alterations in visual cortical activation and connectivity with prefrontal cortex during working memory updating in major depressive disorder. *NeuroImage Clin.* 14, 43–53. doi: 10.1016/j.nicl.2017.01.004
- Lemche, E., Surguladze, S. A., Giampietro, V. P., Anilkumar, A., Brammer, M. J., Sierra, M., et al. (2007). Limbic and prefrontal responses to facial emotion expressions in depersonalization. *Neuroreport* 18, 473–477. doi: 10.1097/WNR.0b013e328057deb3
- Li, G., Liu, Y., Zheng, Y., Li, D., Liang, X., Chen, Y., et al. (2020). Large-scale dynamic causal modeling of major depressive disorder based on resting-state functional magnetic resonance imaging. *Hum. Brain Mapp.* 41, 865–881. doi: 10.1002/hbm.24845
- Liu, J., Fan, Y., Zeng, L.-L., Liu, B., Yumeng, J., Wang, M., et al. (2021). The neuroprogressive nature of major depressive disorder: evidence from an intrinsic connectome analysis. *Transl. Psychiatry* 11:102. doi: 10.1038/s41398-021-01227-8
- Liu, D.-Y., Xuan, J., Gao, Y., Han, J.-F., Li, Z., Xi-Wen, H., et al. (2022). From molecular to behavior: higher order occipital cortex in major depressive disorder. *Cereb. Cortex* 32, 2129–2139. doi: 10.1093/cercor/bhab343
- Liu, L., Zeng, L.-L., Li, Y., Ma, Q., Li, B., Shen, H., et al. (2012). Altered cerebellar functional connectivity with intrinsic connectivity networks in adults with major depressive disorder. *PLoS One* 7:e39516. doi: 10.1371/journal.pone.0039516
- Lu, F., Cui, Q., Huang, X., Li, L., Duan, X., Chen, H., et al. (2020). Anomalous intrinsic connectivity within and between visual and auditory networks in major depressive disorder. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 100:109889. doi: 10.1016/j.pnpbp.2020.109889
- Nigatu, Y. T., Bültmann, U., and Sijmen, A. BMC Public Health Reijneveld (2015). The prospective association between obesity and major depression in the general population: does single or recurrent episode matter? *BMC Public Health* 15, 1–8. doi: 10.1186/s12889-015-1682-9
- Pang, Y., Zhang, H., Cui, Q., Yang, Q., Fengmei, L., Chen, H., et al. (2020). Combined static and dynamic functional connectivity signatures differentiating bipolar depression from major depressive disorder. *Aust. N. Z. J. Psychiatry* 54, 832–842. doi: 10.1177/0004867420924089
- Portella, M. J., de Diego-Adelino, J., Gómez-Ansón, B., Morgan-Ferrando, R., Vives, Y., Puigdemont, D., et al. (2011). Ventromedial prefrontal spectroscopic abnormalities over the course of depression: a comparison among first episode, remitted recurrent and chronic patients. *J. Psychiatr. Res.* 45, 427–434. doi: 10.1016/j.jpsychires.2010.08.010
- Ray, D., Bezmaternyykh, D., Mel'nikov, M., Friston, K. J., and Das, M. (2021). Altered effective connectivity in sensorimotor cortices is a signature of severity and clinical course in depression. *Proc. Natl. Acad. Sci.* 118:e2105730118. doi: 10.1073/pnas.2105730118
- Roca, M., Armengol, S., García-García, M., Rodríguez-Bayón, A., Ballesta, I., Serrano, M. J., et al. (2011). Clinical differences between first and recurrent episodes in depressive patients. *Compr. Psychiatry* 52, 26–32. doi: 10.1016/j.comppsy.2010.04.011
- Rosa, M. J., Portugal, L., Hahn, T., Fallgatter, A. J., Garrido, M. I., Shawe-Taylor, J., et al. (2015). Sparse network-based models for patient classification using fMRI. *NeuroImage* 105, 493–506. doi: 10.1016/j.neuroimage.2014.11.021
- Sambataro, F., Visintin, E., Doerig, N., Brakowski, J., Holtforth, M. G., Seifritz, E., et al. (2017). Altered dynamics of brain connectivity in major depressive disorder at-rest and during task performance. *Psychiatry Res. Neuroimaging* 259, 1–9. doi: 10.1016/j.psychres.2016.11.001
- Schlösser, R. G. M., Wagner, G., Koch, K., Dahnke, R., Reichenbach, J. R., and Sauer, H. (2008). Fronto-cingulate effective connectivity in major depression: a study with fMRI and dynamic causal modeling. *NeuroImage* 43, 645–655. doi: 10.1016/j.neuroimage.2008.08.002
- Seminowicz, D. A., Mayberg, H. S., McIntosh, A. R., Goldapple, K., Kennedy, S., Segal, Z., et al. (2004). Limbic–frontal circuitry in major depression: a path modeling metanalysis. *NeuroImage* 22, 409–418. doi: 10.1016/j.neuroimage.2004.01.015
- Sheng, W., Cui, Q., Jiang, K., Chen, Y., Tang, Q., Wang, C., et al. (2022). Individual variation in brain network topology is linked to course of illness in major depressive disorder. *Cereb. Cortex* 32, 5301–5310. doi: 10.1093/cercor/bhac015
- Su, L.-D., Fang-Xiao, X., Wang, X.-T., Cai, X.-Y., and Shen, Y. (2021). Cerebellar dysfunction, cerebro-cerebellar connectivity and autism spectrum disorders. *Neuroscience* 462, 320–327. doi: 10.1016/j.neuroscience.2020.05.028
- Sun, J., Chen, L., He, J., Zhongming, D., Ma, Y., Wang, Z., et al. (2022a). Altered brain function in first-episode and recurrent depression: a resting-state functional magnetic resonance imaging study. *Front. Neurosci.* 16:876121. doi: 10.3389/fnins.2022.876121
- Sun, J., Zhongming, D., Ma, Y., Chen, L., Wang, Z., Guo, C., et al. (2022b). Altered functional connectivity in first-episode and recurrent depression: a resting-state functional magnetic resonance imaging study. *Front. Neurol.* 13:1822. doi: 10.3389/fneur.2022.922207
- Wang, Y., Chen, X., Liu, R., Zhang, Z., Zhou, J., Feng, Y., et al. (2022). Disrupted effective connectivity of the default, salience and dorsal attention networks in major depressive disorder: a study using spectral dynamic causal modelling of resting-state fMRI. *J. Psychiatry Neurosci.* 47, E421–E434. doi: 10.1503/jpn.220038
- Wei, M., Qin, J., Yan, R., Bi, K., Liu, C., Yao, Z., et al. (2015). Association of resting-state network dysfunction with their dynamics of inter-network interactions in depression. *J. Affect. Disord.* 174, 527–534. doi: 10.1016/j.jad.2014.12.020
- West, Brady T, Welch, Kathleen B, and Galecki, Andrzej T. (2022). *Linear mixed models: a practical guide using statistical software* (Crc Press), Boca Raton, FL.
- Yan, C.-G., Chen, X., Li, L., Castellanos, F. X., Bai, T.-J., Bo, Q.-J., et al. (2019). Reduced default mode network functional connectivity in patients with recurrent major depressive disorder. *Proc. Natl. Acad. Sci.* 116, 9078–9083. doi: 10.1073/pnas.1900390116
- Yang, T., Wang, H., Dai, H., Hui, J., Zhang, J., Li, J., et al. (2023). The fNIRS evaluation of frontal and temporal lobe cortical activation in Chinese first-episode medication-naïve and recurrent depression during a verbal fluency task. *Front. Psych.* 14:1132666. doi: 10.3389/fpsy.2023.1132666
- Yin, Y., Wang, M., Wang, Z., Xie, C., Zhang, H., Zhang, H., et al. (2018). Decreased cerebral blood flow in the primary motor cortex in major depressive disorder with psychomotor retardation. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 81, 438–444. doi: 10.1016/j.pnpbp.2017.08.013
- Yu, M., Linn, K. A., Shinohara, R. T., Oathes, D. J., Cook, P. A., Duprat, R., et al. (2019). Childhood trauma history is linked to abnormal brain connectivity in major depression. *Proc. Natl. Acad. Sci.* 116, 8582–8590. doi: 10.1073/pnas.1900801116
- Zhang, C., Jing, H., Yan, H., Li, X., Liang, J., Zhang, Q., et al. (2023). Disrupted interhemispheric coordination of sensory-motor networks and insula in major depressive disorder. *Front. Neurosci.* 17:1135337. doi: 10.3389/fnins.2023.1135337
- Zhao, Y., Zhang, F., Zhang, W., Chen, L., Chen, Z., Lui, S., et al. (2021). Decoupling of gray and white matter functional networks in medication-naïve patients with major depressive disorder. *J. Magn. Reson. Imaging* 53, 742–752. doi: 10.1002/jmri.27392