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RESEARCH ARTICLE

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Increased functional interaction within frontoparietal network during working memory task in major depressive disorder

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Abstract

Abnormal fronto-parietal activation has been suggested as a neural underpinning of the working memory (WM) deficits in major depressive disorder (MDD). However, the potential interaction within the frontoparietal network during WM processing in MDD remains unclear. This study aimed to examine the role of abnormal functional interactions within frontoparietal network in the neuropathological mechanisms of WM deficits in MDD. A total of 40 MDD patients and 47 demographic matched healthy controls (HCs) were included. Functional magnetic resonance imaging and behavioral data were collected during numeric n-back tasks. The psychophysiological interaction and dynamic causal modelling methods were applied to investigate the connectivity within the frontoparietal network in MDD during n-back tasks. The psychophysiological interaction analysis revealed that MDD patients showed increased functional connectivity between the right inferior parietal lobule (IPL) and the right dorsolateral prefrontal cortex (dlPFC) compared with HCs during the 2-back task. The dynamic causal modelling analysis revealed that MDD patients had significantly increased forward modulation connectivity from the right IPL to the right dlPFC than HCs during the 2-back task. Partial correlation was used to calculate the relationship between connective parameters and psychological variables in the MDD group, which showed that the effective connectivity from right IPL to right dlPFC was correlated negatively with the sensitivity index d' of WM performances and positively with the depressive severity in MDD group. In conclusion, the abnormal functional and effective connectivity between frontal and parietal regions might contribute to explain the neuropathological mechanism of working memory deficits in major depressive disorder.

KEYWORDS
effective connectivity, frontoparietal network, functional connectivity, major depressive disorder, working memory

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1 | INTRODUCTION

Major depressive disorder (MDD) is a prevalent and disabling psychiatric disease associated with high incidence and mortality (Huang et al., 2019; Spellman & Liston, 2020). Cognitive deficits have been recognized as one of the important features of MDD, such as impaired working memory (WM) or attention and reduced executive functioning (Ahern & Semkovska, 2017; Knight & Baune, 2018). As WM is the basis for many cognitive processes and day-to-day activities (Wager & Smith, 2003), the difficulties in updating the contents of WM might hinder the removal of negative information and contribute to disturbances in emotion regulation, which facilitates perseverative thinking (e.g., rumination) and increases the risk for depression onset and recurrence (Joormann & Quinn, 2014; Le, Borghi, Kujawa, Klein, & Leung, 2017; Yüksel et al., 2018). Therefore, understanding the WM deficits in MDD is of paramount importance for clarifying the pathogenesis of MDD.

Numerous functional magnetic resonance imaging (fMRI) studies with n-back and Sternberg task have explored the neural mechanism of WM processing in MDD and revealed abnormal task-related brain activation in frontal regions (namely, orbital, medial, dorsolateral and ventrolateral prefrontal cortex as well as the anterior cingulate cortex), parietal cortex, parts of the temporal regions, and insula in MDD (Gärtner et al., 2018; Sankar, Adams, Costafreda, Marangell, & Fu, 2017; Smith et al., 2018; Wang et al., 2015; Yüksel et al., 2018). Some studies also found altered modulation at cortical regions which were involved in higher-order executive functions during WM processing in MDD, especially in the dorsolateral prefrontal cortex (dlPFC) and parietal cortex (Gao et al., 2020; Smith et al., 2018; Tan et al., 2020). The dlPFC plays an important role in encoding, manipulating information, and setting attentional priorities (D'Esposito, Postle, & Rypma, 2000; Geiger et al., 2018), while the parietal cortex is associated with storing, retrieving information, and maintaining attentional focus (Guerin & Miller, 2011; Hakun & Ravizza, 2016). Therefore, the abnormal fronto-parietal activation found in previous task-based studies might be the neural underpinnings of WM deficits in MDD (Kerestes et al., 2012; Mannie, Harmer, Cowen, & Norbury, 2010; Tan et al., 2020). However, the assessment of regional brain engagement in frontal and parietal regions cannot sufficiently capture the dynamic brain activities within frontoparietal network during WM task. Previous studies have suggested that the functional interaction of frontal and parietal regions is critical for successful WM processing (Infante et al., 2017; Jung et al., 2018; Schmidt et al., 2014; Vilgis, Chen, Silk, Cunnington, & Vance, 2014), while the specific mechanism by which abnormal interaction within the frontoparietal network contributing to the deficits in WM in MDD remains unclear.

Resting state fMRI studies have reported reduced functional connectivity between prefrontal and parietal regions in MDD (Balaev, Orlov, Petrushevsky, & Martynova, 2018; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Müller, Cieslik, Laird, Fox, & Eickhoff, 2013), but do not specify the abnormalities that emerge during stimulus processing in MDD (Biswal, Yetkin, Haughton, & Hyde, 1995). Exploring functional interaction within brain regions during WM task will help to understand the relationship between task requirements and brain neurophysiological responses (Geiger et al., 2018; Nielsen et al., 2017). At present, psychophysiological interactions (PPIs) and dynamic causal modeling (DCM) are two valid and mutually complementary methods to analyze the task-related functional interaction among brain regions. The PPIs method is data-driven and allows for exploration of context-dependent connectivity between brain regions in an experimental task (Friston et al., 1997; Nimarko et al., 2020), while the DCM is model-driven and enables the estimation of effective connectivity through which one neural system exerts influence on another, which provides information about the connectivity directionality or causality across potentially disrupted neural networks (Friston, Harrison, & Penny, 2003; Oliva et al., 2020). Therefore, in this study, both data-driven (functional connectivity) and model-driven (effective connectivity) approaches would be used to explore the neuropathological mechanism of WM deficits in MDD patients.

As far as we know, there have been only a few studies investigating functional connectivity during WM task in MDD. Garrett et al. (2011) found enhanced functional connectivity between right temporoparietal junction and left dlPFC during WM task in psychotic MDD. Le et al. (2017) demonstrated increased functional connectivity between left middle frontal gyrus and visual cortical (right parahippocampal place area) during WM updating processing in MDD. To date, however, there are no DCM studies attempting to explore potential alteration of effective connectivity in the context of WM in MDD patients. While a few fMRI studies have used DCM to examine the effective connectivity during attentive or emotional task in MDD patients, and found disturbed effective connectivity within fronto-cingulate (Schlösser et al., 2008), visuo-attentional network (Desseilles et al., 2011), fronto-temporal (Goulden et al., 2012), and amygdala-anterior cingulate cortex (Musgrove et al., 2015). Meanwhile, researchers have struggled to explore effective connectivity within frontoparietal network during memory tasks in healthy individuals, and got some inconsistent results. Ma et al. (2012) found increased effective connectivity from posterior parietal cortex to inferior frontal cortex in higher digit load task. Dima, Jogia, and Frangou (2014) also found increased forward (from parietal cortex to dlPFC) modulation and greater right hemisphere contribution as memory load increased during a n-back task. However, Heinzel, Lorenz, Duong, Rapp, and Deserno (2017) revealed increased load-dependent modulation from dlPFC to parietal cortex as memory load increased during a n-back task in younger adults. The above studies suggested that frontoparietal network is a crucial component of the WM processing, and it is necessary to explore the effective connectivity within frontoparietal network in MDD during WM task. Up to now, however, no relevant researches have focused on the effective connectivity within frontoparietal network during WM processing in MDD.

Therefore, this study aimed to investigate the role of abnormal functional interaction within frontoparietal network in the neuropathological mechanisms of WM deficits in MDD. Both data-driven PPI and model-driven DCM methods were combined to examine the connectivity of frontoparietal network during WM processing, and the

associations between connective parameters and WM performances of MDD patients were also assessed.

2 | METHODS AND MATERIALS

2.1 | Participants

MDD patients were recruited from the outpatients of the Second Xiangya Hospital, Central South University, Changsha, China. Gender-, age-, and education- matched healthy controls (HCs) were recruited from the surrounding community by posters and advertisements. The study protocol was approved by the ethics committee of Second Xiangya Hospital, Central South University. Each participant was aware of the study's purpose and provided an informed consent form.

The diagnosis of MDD was conducted by two experienced psychiatrists using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). The exclusion criteria for MDD group were comorbidity with other psychiatric disorders (e.g., schizophrenia, schizoaffective, bipolar disorder, substance abuse or substance dependence), history of neurological disease (e.g., seizure disorder), history of brain injury, current physical diseases (e.g., severe diabetes), or any contraindications to MRI. The exclusion criteria for HC group were any history of psychiatric disorders (e.g., MDD, schizophrenia, schizoaffective, bipolar disorder, substance abuse or substance dependence), history of neurological disease (e.g., seizure disorder), history of brain injury, current physical diseases (e.g., severe diabetes), or any contraindications to MRI. Finally, a total of 45 MDD patients and 50 HCs were recruited. Five patients in the MDD group were taking selective serotonin re-uptake inhibitors as antidepressant medication.

2.2 | Psychometric instruments

2.2.1 | Structured clinical interview for DSM-IV (SCID)

As a semi-structured interview, the SCID has been the "gold standard" to diagnose or screen mental diseases in DSM-IV by using its standardized clinician-directed queries of relevant symptomatic domains (First & Gibbon, 2004). In this study, the SCID was applied to diagnose MDD and exclude other mental disorders, such as bipolar disorder and schizophrenia. Good inter-rater reliability of the Chinese SCID was evidenced in this study, with all intraclass correlation coefficients above .75.

2.2.2 | Center for Epidemiological Studies Depression Scale (CES-D)

The 20-item CES-D was used to assess participants' depression levels (Radloff, 1977). Each item is scored on a 4-point Likert scale, ranging from 1 (never) to 4 (very often), and the total score of CES-D is from 20 to 80. The Chinese version of CES-D has shown good psychometric properties (Wang et al., 2013).

2.2.3 | State-trait anxiety inventory (STAI)

The STAI is a self-report questionnaire (Spielberger, 1983), including state anxiety inventory (SAI) and trait anxiety inventory (TAI). Each inventory includes 20 items, and each item is scored on a 4-point Likert scale (1 = never, 4 = always). In the current study, only the SAI was adopted, whose total score is from 20 to 80. The Chinese version of SAI has shown acceptable reliability and validity (Shek, 1993).

2.3 | Working memory task

A modified version of the numeric n-back WM task was conducted similarly to a previous study (Liu et al., 2017), see Figure 1. Stimuli were projected on a computer screen using E-prime 2.0, and participants were required to match the target stimulus using a four-button response box. This task included two conditions: 0-back condition, in which participants were instructed to press a key in response to the number (1–4) presented; 2-back condition, in which participants needed to press the button corresponding to number (1–4) displayed in two trials before the current one. There were 8 blocks per condition. Each block contained 16 trials with a number presentation for 500 ms and interstimulus interval of 1,500 ms. When participants completed each block, they were allowed to rest for 16 s, looking at a fixed cross in the center of the screen. And this resting period was regarded as baseline (Wu et al., 2014). The total duration of the experiment was 12 min 56 s.

2.4 | Image data acquisition and processing

2.4.1 | Image data acquisition

The MRI images were acquired on a 3.0 T Siemens Magnetom Skyra scanner. A high-resolution T1-weighted structural scan with a three-dimensional spoiled gradient recalled sequence was used to exclude structural abnormalities and for spatial normalization for each participant. The T1 parameters were as follows: repetition time (TR) = 1900 ms, echo time (TE) = 2.01 ms, flip angle = 9°, matrix = 256 × 256, voxel size = 1 × 1 × 1 mm^3, field of view (FOV) = 256 × 256 mm, slice thickness = 1.0 mm. When participants were performing the n-back task, functional images were acquired with an echo-planar imaging sequence (slice = 32, TR = 2000 ms, TE = 28 ms, flip angle = 90°, matrix = 64 × 64, voxel size = 3.3 × 3.3 × 4.0 mm^3, FOV = 210 × 210, slice thickness = mm, slice gap = 4.0 mm).

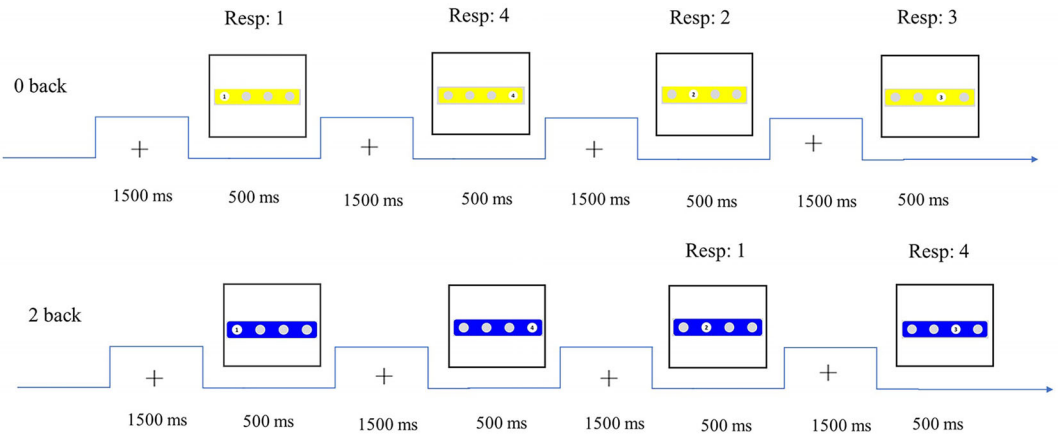

FIGURE 1 The paradigm of n-back task. For 0-back, the task required a simple button press in response to the number displayed. For 2-back, participants pressed the key corresponding to the number presented two trials before the current one

2.4.2 | Image data preprocessing

All fMRI image preprocessing was conducted in the Data Processing Assistant for Resting-State fMRI (DPARSF, Chao-Gan & Yu-Feng, 2010). Preprocessing included slice timing correction, realignment and motion correction by a maximum head movement with three translation and three rotation parameters, spatial normalization with the standard space template of Montreal Neurologic Institute (resampling into $3 \times 3 \times 3$ mm^3 voxels), and smoothing with an 8-mm full-width half maximum Gaussian kernel. Data from five MDD and three HC participants were excluded due to poor image quality or excessive head movements. The excluded five MDD patients were not taking medication. The final analysis included 40 MDD patients and 47 HCs. To reduce residual motion for the connectivity analyses, this study calculated the mean framewise displacements (FD) of each participant and compared group differences in head movement (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), which showed that MDD group and HC group did not differ in mean FD (independent two-sample t test: $t = -0.77$, $p = .45$).

For within-subject statistical analysis, individual contrast images for 0-back versus baseline and 2-back versus baseline were computed, respectively. The 2-back > 0-back contrast was also calculated to identify regions activated by the WM load across participants (family-wise error correction, $p < .05$). This contrast was done across participants to generate the same coordinates for the MDD and HC groups, which improve the precision for the subsequent group comparisons of functional connectivity and effective connectivity (Nielsen et al., 2017)."

2.4.3 | Psychophysiological interaction analyses

Implemented in statistical parametric mapping software package (SPM12; http://www.fil.ion.ucl.ac.uk/spm/), the PPI analyses were performed to measure the correlations of time series of volumes of interest (VOIs) with other brain regions. The study found that significant WM load (2-back >0-back contrast) across all participants existed in right inferior parietal lobule (IPL) and right dlPFC. Therefore, these two regions were selected as VOIs for further functional connectivity analyses. Given that these two regions surpassing our threshold were located in the right hemisphere, previous studies also supported that right hemisphere dominance was correlated with increasing WM load (Dima et al., 2014; Schmidt et al., 2014), we focused our analysis in right hemisphere only. For each individual, the time series of VOIs were extracted from peak coordinates of the right dlPFC ($x = 27$, $y = 6$, $z = 54$) and right IPL ($x = 54$, $y = -36$, $z = 42$) at uncorrected threshold $p < .001$. Each VOI was extracted from the sphere of 6 mm radius around the local maxima. The design matrix of PPI consisted of three main regressors: the physiological variable that represents the time series from the VOIs (e.g., right dlPFC, and right IPL), the psychological variable which represents the task conditions (e.g., 2-back and 0-back), and the PPI variable. Fisher's z transformation was used to transform the resulting contrast into a z-score for subsequent group level analyses. Functional connectivity between each seed and other brain areas was analyzed separately. A cluster-level false discovery rate correction $p < .05$ with a voxel-level threshold of $p < .001$ was used.

2.4.4 | Dynamic causal modeling analyses

The DCM in SPM12 was used to analyze the effect of WM task on effective connectivity among modeled brain regions, and explore whether the connectivity strengths of modulations could distinguish the MDD patients from HCs. More specifically, DCM for fMRI was used to analyze input-state-output neural states across a network of brain regions (Friston et al., 2003). Inputs correspond to external stimulus functions, states include neuronal and neurophysiological variables needed to form outputs, while outputs correspond to hemodynamic responses in fMRI studies. Inputs can produce responses in two ways. First, inputs elicit response directly, through influencing on specific anatomical nodes. For example, sensory input

could be modeled as causing direct responses in early visual or auditory cortices. Second, inputs exert their effect vicariously, through a modulation of the coupling among nodes. In DCM, the endogenous coupling between two regions in the absence of task stimulus is termed as intrinsic connections, while the impact of experimental conditions on coupling among nodes is regarded as modulations. Generally, the direct influence of experimental stimuli on specific regions can be modeled as driving input. In this study, the visual n-back task firstly activated the visual cortex (VC), therefore the VC was modeled as the driving input region.

Volumes of interest selection and time series extraction

The VOIs were selected for the following rationale: (a) the current results found significant effects of WM load in frontal and parietal areas; (b) previous neuroimaging studies found that the abnormal fronto-parietal activation might be the neural underpinnings of WM deficits in MDD (Kerestes et al., 2012; Mannie et al., 2010; Tan et al., 2020); (c) previous DCM studies of WM tasks in HCs found that frontoparietal network is a crucial component of WM processing (Dima et al., 2014; Ma et al., 2012; Schmidt et al., 2014); (d) the VC was activated in the n-back tasks. Based on these criteria, right IPL, right dlPFC, and primary VC were selected as the VOIs for DCM analyses in this study.

The coordinates of right IPL and right dlPFC were defined by the significant activation clusters, which were obtained by effect of 2-back > 0-back contrast across all participants. For DCM analyses, the VOI extraction of the right IPL and right dlPFC were the same as PPI analyses. The peak coordinate of VC ($x = 18$, $y = -78$, $z = 9$) was specified by visual contrast (2-back and 0-back to baseline) in the task and combined with an anatomical mask of Brodmann area 17. The VOIs were surrounded with 6 mm eigenvariate spheres by the MNI coordinates of selected peak.''

Model space

The modulatory direction of task condition affecting the frontoparietal connectivity was divided into three model families: forward (from right IPL to right dlPFC), backward (from right dlPFC to right IPL), or bidirectional. Each model family contained 16 candidate models according to modulatory among the right dlPFC, right IPL and VC of bidirectional and unidirectional experimental. Therefore, there were 48 dynamic causal models for each participant (Figure 2). We assessed model parameters using a one-state, bilinear, deterministic DCM.

Bayesian model selection and averaging

To compare models, we performed Bayesian model selection with a random-model effects approach, producing expected model probabilities and exceedance probabilities (EPs) for each model. The EPs, representing the probability that one model is more likely than the others, were used to choose the best model family.

For statistical comparison of the model parameters, Bayesian model averaging (BMA) was conducted to obtain averages of DCM parameter estimates across the entire model space, weighted by posterior model probabilities for each model (Penny et al., 2010). Models with higher posterior probability devoted more to estimation of the marginal posterior. The posterior distribution was extracted from the averaged DCM parameters to evaluate group differences in intrinsic connections and modulation parameters. The results were reported at a Bonferroni-corrected threshold for six modulatory parameters and an uncorrected threshold of $p < .05$.

2.5 | Statistical analysis

In SPSS 25 software (SPSS Inc., Chicago, IL), Chi-squared tests and two-sample *t*-tests were used to compare the differences in demographic and clinical characteristics between MDD patients and HCs. Cohen's *d* and η^2 was used to calculate the effect size.

Behavioral variables were calculated by 2 (group: MDD vs. HC) × 2 (WM load: 2-back vs. 0-back) repeated-measures ANOVA followed by post hoc Bonferroni correction, with group as a between-subject factor and task load as a within subject factor. According to the signal detection theory, the sensitivity index d' could be applied to present the WM performances objectively (Macmillan & Kaplan, 1985), with a higher value indicating a higher level of accuracy in the n-back task. First, hits and false alarms for each condition of WM task were measured for each subject. Second, probabilities of hits and false alarms were transformed into z-scores using the inverse cumulative distribution function in MATLAB (icdf). Then, sensitivity index d' was computed using the following equation from Wickens (2002): $d' = z(\text{probability}_{\text{hits}}) - z(\text{probability}_{\text{false alarms}})$.

In terms of fMRI data, one-sample *t* tests were applied to analyze the differences within group, and two-sample *t* tests were used to compare differences between the two groups with age, gender, years of education, and SAI scores as covariate variables in SPM12. Partial correlation was conducted to analyze the relationship between connective parameter showing significant group differences and the WM performances after controlling for age, gender, years of education, CES-D scores, and SAI scores in the MDD group. Partial correlation was also conducted between connective parameter showing significant group differences and the depressive severity in the MDD group with age, gender, years of education, and SAI scores being controlled.

3 | RESULTS

3.1 | Demographic, clinical characteristics, and task performances

The final analysis included 40 MDD patients and 47 HCs. As shown in Table 1, there were no group differences in gender, age, and years of education. The MDD group had significantly higher scores of CES-D ($t = 15.46$, $p < .001$) and SAI ($t = 12.96$, $p < .001$) than the HC group. Among the MDD group, five of them were taking antidepressant medication. After removing these five medicated patients, the drug-naïve MDD group and the HC group were still matched in gender, age, and years (see Table S1).

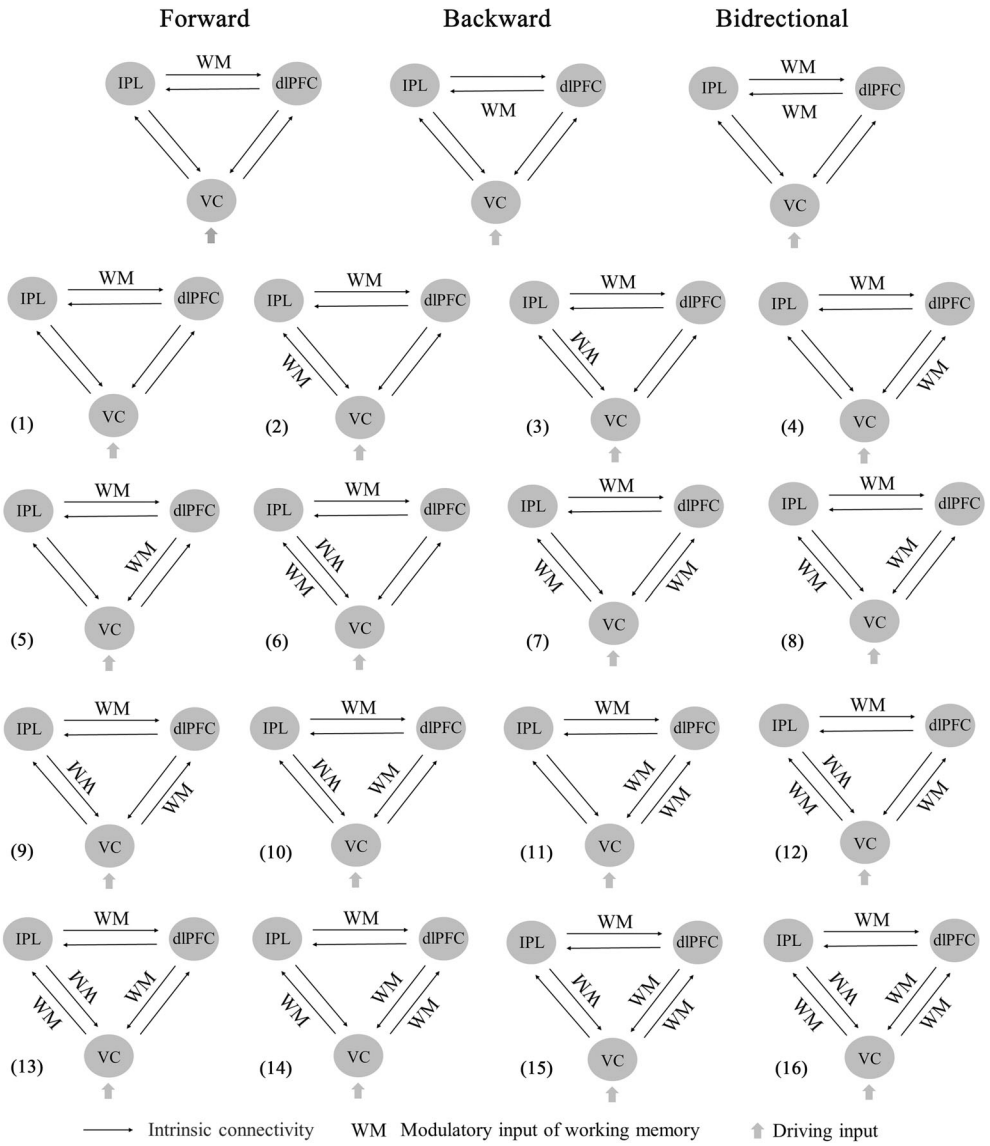

FIGURE 2 Examples of model space of the DCM analysis (forward model shown here). The top row shows the three model families defining the partitions of the model space. The four bottom rows show the 16-model subspace generated by including all possible modulations (forward model shown here). DCM, dynamic causal modeling; dlPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobule; WM, working memory; VC, visual cortex

WM performances for HC and MDD groups under each condition were shown in Table 2. On mean reaction time, significant group difference (MDD > HC, $F_{(1,85)} = 10.62$, $p = .002$, $\eta^2 = 0.11$), significant main effect of WM load (2-back >0-back, $F_{(1,85)} = 34.08$, $p < .001$, $\eta^2 = 0.29$) were observed, while no significant group × WM load interaction ($F_{(1,85)} = 3.65$, $p = .06$) was found. On accuracy, significant group difference (MDD < HC, $F_{(1,85)} = 12.76$, $p = .001$, $\eta^2 = .13$), significant main effect of WM load (2-back < 0-back, $F_{(1,85)} = 81.84$, $p < .001$, $\eta^2 = 0.49$), and significant group × WM load interaction ($F_{(1,85)} = 11.54$, $p = .001$, $\eta^2 = 0.12$) were observed. Post hoc analysis showed that MDD group had lower accuracy than HC group during 2-back task ($F_{(1,85)} = 15.27$, $p < .001$, $\eta^2 = 0.15$), while no significant group difference during 0-back task was found; both MDD ($F_{(1,85)} = 71.66$, $p < .001$, $\eta^2 = 0.46$) and HC groups ($F_{(1,85)} = 17.36$, $p < .001$, $\eta^2 = 0.17$) had lower accuracies in 2-back compared to 0-back. On sensitivity index d', significant group difference (MDD < HC, $F_{(1,85)} = 5.00$, $p = .028$, $\eta^2 = 0.06$), significant main effect of WM load (2-back < 0-back, $F_{(1,85)} = 86.39$, $p < .001$, $\eta^2 = 0.50$) were observed, while no significant group × WM load interaction ($F_{(1,85)} = 3.24$, $p = .075$) was found.

3.2 | Brain activation during the n-back task

The task analysis showed a significant activation of WM load (2-back > 0-back) in the right dlPFC and right IPL, a significant deactivation of WM load (2-back < 0-back) in the left medial frontal gyrus, right posterior cingulate gyrus, and left angular gyrus (Table 3, Figure 3). However, no significant group differences in activation were observed ($p > .05$).

3.3 | Functional connectivity during working memory task

With right IPL as a seed region, the MDD patients showed significantly increased functional connectivity between the right IPL and

TABLE 1 Comparison of the demographic and clinical characteristics between HC and MDD group

Characteristic	HC group ($N = 47$)	MDD group ($N = 40$)	x^2/t	p	|Cohen's d|
Age (years)	20.98 ± 2.34	19.98 ± 4.70	1.23	.23	–
Sex (male/female)	19/28	12/28	1.02	.31	–
Education (years)	14.1 ± 1.71	13.2 ± 2.41	1.98	.052	–
FD (mm)	0.13 ± 0.06	0.14 ± 0.07	−0.77	.45	–
CES-D	32.91 ± 8.37	62.30 ± 9.35	−15.46	<.001	3.31
SAI	37.91 ± 7.57	61.23 ± 9.20	−12.96	<.001	2.77

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scales; |Cohen's d|, absolute value of Cohen's d; |Cohen's d| > 0.8, large effect size; FD, framewise displacements; HC, healthy controls; MDD, major depressive disorder; SAI, state anxiety inventory.

TABLE 2 WM performances for n-back tasks in HC and MDD groups

	HC group ($n = 47$)		MDD group ($n = 40$)	
	0-back	2-back	0-back	2-back
Reaction time (ms)	355.53 ± 79.85	415.38 ± 98.78	371.52 ± 97.50	489.55 ± 106.53
Accuracy (%)	93.60 ± 0.07	84.53 ± 0.10	91.77 ± 0.09	71.80 ± 0.19
Sensitivity index d'	3.59 ± 1.29	2.23 ± 0.91	3.43 ± 1.52	1.42 ± 1.49

Note: Sensitivity index $d' = z(\text{probability}_{\text{hits}}) - z(\text{probability}_{\text{false alarms}})$.
Abbreviations: HC, healthy control; MDD, major depressive disorder.

TABLE 3 Brain activations in WM load during the n-back task across all participants

			MNI coordinates				
Region	BA	Side	x	y	z	k	t
2-back > 0-back							
Dorsolateral prefrontal cortex	9	R	27	6	54	1,581	9.38
Inferior parietal lobule	40	R	54	−36	42	931	7.33
2-back < 0-back							
Medial frontal gyrus	10	L	−12	45	45	1,003	−9.29
Posterior cingulate gyrus	31	R	6	−48	18	503	−8.12
Angular gyrus	39	L	−51	−66	30	139	−6.25

Abbreviations: BA, Brodmann area; k, cluster extent; L, left; MNI, Montreal Neurological Institute; R, right; WM, working memory.

right dlPFC compared with HCs during the 2-back task (Table 4, Figure 3). With right dlPFC as a seed region, no significant group differences of functional connectivity were found during the 2-back condition. For the 0-back task, no significant group differences of functional connectivity were found with right IPL and right dlPFC as seeds.

3.4 | Effective connectivity during working memory task

As shown in Figure 4, in all participants, the comparison of model evidence among the three families (backward, forward, or bidirectional modulation of frontoparietal connections) during 2-back task revealed that the forward family (EP = 0.73) was superior the other two families. Bayesian model selection for each group separately during 2-back task showed that in the HC group, the forward family (EP = 0.78) outperformed the others. In the MDD group, however, the backward family (EP = 0.64) explained the data best. Due to the different results between the two groups in selecting the model family, BMA inferences over all 48 model spaces were conducted to prevent bias of model selection.

In the HC group, the 2-back task modulatory connectivity from right IPL to right dlPFC was significant and negative. In the MDD group, the 2-back modulation connectivities from right IPL to right dlPFC and from VC to right IPL were both significant and positive. The modulation from the right IPL to the right dlPFC showed a significant group difference ($t = -3.06$, $df = 85$, $p = .003$; Bonferroni corrected), and MDD patients displayed significantly increased modulation than HCs during 2-back task (Table 5, Figure 5). No significant group differences of effective connectivity were found during 0-back task.

The differences between the drug-naïve MDD group and HC group in WM performances, brain activation, functional connectivity, and effective connectivity during n-back task were similar to the

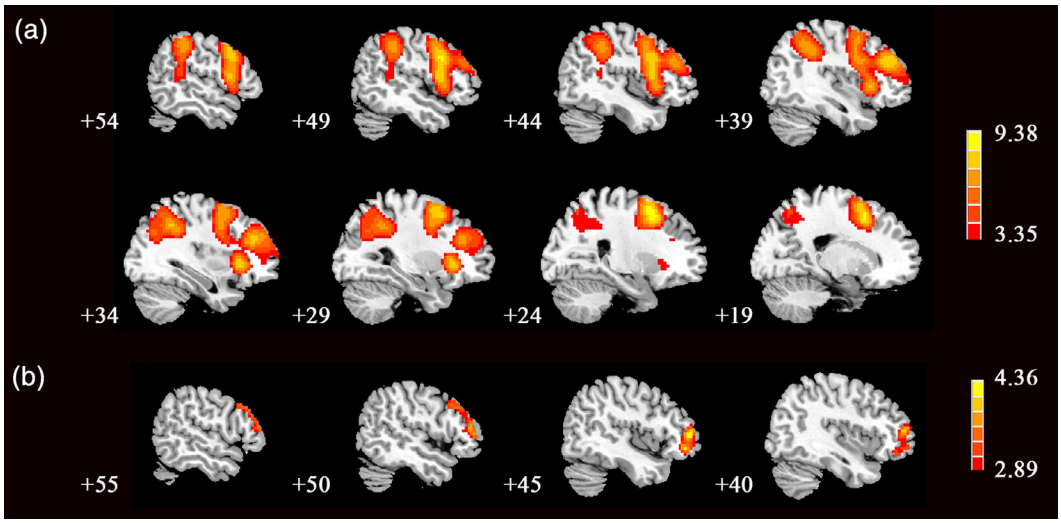

FIGURE 3 Brain activation and functional connectivity during n back task. (a) Frontoparietal activation during working memory load (displayed at PFWE < 0.05 for the 2-back > 0-back contrast). (b) Significant group differences in PPIs of the right IPL with right dlPFC in the 2-back task (MDD patients > HCs). dlPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobule; MDD, major depressive disorder; PPL, psychophysiological interactions

TABLE 4 Comparison of PPIs of right IPL between HC and MDD groups during 2-back task

Region	BA	Side	MNI coordinates			*k*	*t*
			x	*y*	*z*		
MDD > HC Dorsolateral prefrontal cortex	46	R	45	45	3	91	4.36

Abbreviations: BA, Brodmann area; HC, healthy control; IPL, inferior parietal lobule; *k*, cluster extent; L, left; MDD, major depressive disorder; MNI, Montreal Neurological Institute; PPIs, psychophysiological interactions; R, right.

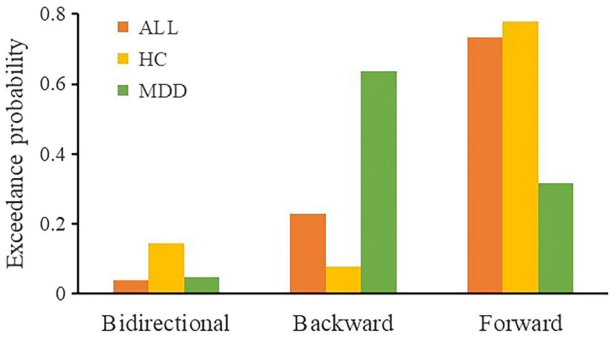

FIGURE 4 Family-wise Bayesian model selection within all participants, as well as HC and MDD group separately. HC, healthy controls; MDD, major depressive disorder

results comparing the MDD group (including drug-naïve and medicated MDD patients) with HC group.

3.5 | Partial correlations between connective parameters and psychological variables

A negative correlation was found between sensitivity index d' and effective connectivity from right IPL to right dlPFC during 2-back task in the MDD group after controlling for age, gender, years of education, CES-D scores and SAI scores ($r = -.352$, $p = .038$). To dissociate attentional and perceptual processes, sensitivity index d' and effective connectivity from right IPL to right dlPFC in the 2-back versus 0-back were calculated, respectively. In the MDD group, there was a negative correlation between cognitive performance assessed with the sensitivity index $d'_{\text{2-back versus 0-back}}$ and effective connectivity$_{\text{2-back versus 0-back}}$ from right IPL to right dlPFC ($r = -.395$, $p = .019$), with age, gender, years of education, CES-D scores, and SAI scores being controlled. No other significant correlations between connective parameters and behavioral variables were found.

A positive correlation was found between depressive severity and effective connectivity from right IPL to right dlPFC during 2-back task in the MDD group ($r = .569$, $p < .001$), with age, gender, years of education, and SAI scores being controlled.

4 | DISCUSSION

To our knowledge, this is the first study combining PPI and DCM of task-related fMRI signals to explore the connectivity characteristics of frontoparietal network during WM task in MDD patients. Our PPI

TABLE 5 Comparison of dynamic causal modeling connection between HC and MDD groups during 2-back task

	HC group		MDD group		Group comparison	
Connection type	**Mean**	***SD***	**Mean**	***SD***	***t***	***p***
Intrinsic connections						
IPL to dlPFC	0.158**	0.227	0.134**	0.175	0.527	.600
IPL to VC	0.052*	0.151	0.047*	0.136	0.173	.863
dlPFC to IPL	0.119**	0.215	0.148**	0.174	−0.667	.507
dlPFC to VC	−0.015	0.170	0.001	0.174	−0.426	.671
VC to IPL	0.040	0.230	0.059	0.225	−0.394	.694
VC to dlPFC	0.031	0.262	−0.017	0.214	0.919	.361
Modulatory connections						
IPL to dlPFC	−0.213*	0.692	0.206*	0.564	−3.060	.003**
IPL to VC	0.010	0.356	0.067	0.427	−0.673	.503
dlPFC to IPL	0.025	0.329	0.020	0.417	0.064	.949
dlPFC to VC	0.015	0.461	0.054	0.680	−0.320	.750
VC to IPL	−0.011	0.893	0.235*	0.700	−1.409	.163
VC to dlPFC	0.124	1.045	−0.071	0.721	0.996	.322

Note: Intrinsic connections: the endogenous coupling between two regions in the absence of task stimulus; Modulatory connections: the impact of 2-back task on the intrinsic connectivity.
Abbreviations: dlPFC, dorsolateral prefrontal cortex; HC, healthy controls; IPL, inferior parietal lobule; MDD, major depressive disorder; VC, visual cortex.
*Significant at $p < .05$ (uncorrected for multiple comparisons).
**Significant at $p < .05$ (Bonferroni corrected for multiple comparisons).

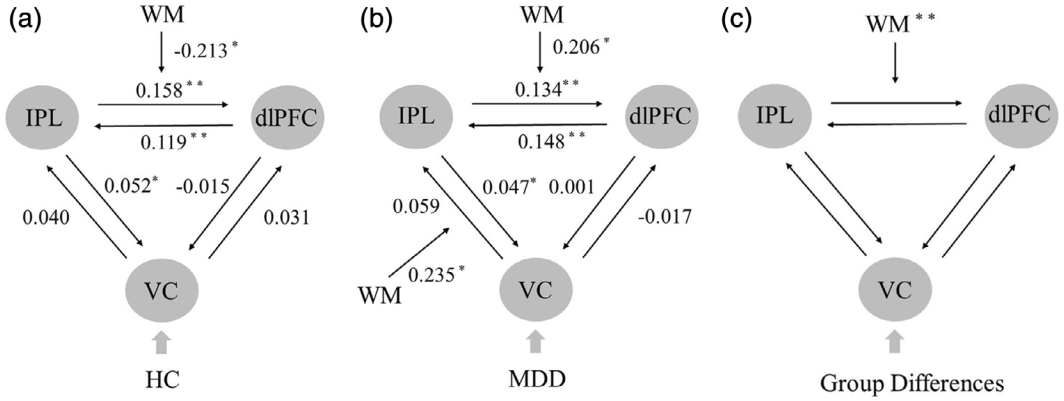

FIGURE 5 Parameter estimates from Bayesian model averaging over the entire model space (i.e., 48 models). (a) The modulatory connectivity from right IPL to right dlPFC was significant and negative in HC group. (b) The modulation connectivity from right IPL to right dlPFC and from VC to right IPL was significant and positive in MDD group. (c) The modulation from right IPL to right dlPFC showed a significant group difference. Modulatory parameters with $p > .05$ are omitted. *Significant at $p < .05$ (uncorrected for multiple comparisons). **Significant at $p < .05$ (Bonferroni corrected for multiple comparisons). dlPFC, dorsolateral prefrontal cortex; HC, healthy controls; IPL, inferior parietal lobule; MDD, major depressive disorder; VC, visual cortex

analyses revealed that MDD patients showed increased functional connectivity between right IPL and right dlPFC compared with HCs during the 2-back task. DCM analyses found that MDD patients had increased forward connectivity from right IPL to right dlPFC compared with HCs during the 2-back task. The connective strength from right IPL to right dlPFC correlated negatively with sensitivity index d' of WM performances, and positively with depressive severity in MDD group. All these findings advance our understanding of the neural brain architecture of WM in MDD.

The MDD group showed significantly higher functional connectivity between right IPL and right dlPFC and increased modulation from right IPL to right dlPFC compared with HC group during the 2-back task. The result of higher functional connectivity between right IPL and right dlPFC in MDD patients is in agreement with previous finding, suggesting that increased functional connectivity between IPL and dlPFC may serve as a neuroimaging marker for cognitive deficit in MDD (Shen et al., 2015). Increased effective connectivity in MDD patients could indicate an enlarged ability to modulate prefrontal brain

activity by ascending parietal afferents during the 2-back task. Our finding of increased modulation from right IPL to right dlPFC during the 2-back task in MDD pointed out the crucial role of parietal areas in driving functional integration in the frontoparietal network during WM task in MDD. Generally, the IPL is activated when attention is focused on external stimuli (Igelström & Graziano, 2017). IPL is also involved in visual–spatial processing during n-back task (Duma et al., 2019), and the dlPFC is relevant for central executive system of WM (Watters, Carpenter, Harris, Korgaonkar, & Williams, 2019). Meanwhile, the connections from the parietal to prefrontal cortex (bottom-up) likely contribute to the encoding of incoming stimuli (Ma et al., 2012; Schmidt et al., 2014), while the connections from the prefrontal to parietal cortex (top-down) may mediate the updating of rules (Gazzaley, Rissman, & D'Esposito, 2004; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005). Thus, the result of increased effective connectivity from right IPL to right dlPFC in this study might suggest that MDD patients have less efficient communication from the parietal to prefrontal cortex, and their bottom-up stimulus encoding might be deficit. Stimulus encoding abnormalities could influence recruitment of attentional resources when novel information being presented, and disrupt ongoing memory information (Bays, Gorgoraptis, Wee, Marshall, & Husain, 2011). It has been proposed that inefficient encoding leads to poor or imprecise internal representations of the information being stored in WM, which is partly responsible for WM deficit in MDD patients (Li et al., 2018; Murphy et al., 2019).

Previous studies have suggested abnormal effective connectivity within frontoparietal network is associated with functional impairment of WM in patients with affective disorder and individuals with psychotic experiences (Dima, Roberts, & Frangou, 2016; Fonville et al., 2015), and the microstructure of frontoparietal network can predict the WM performance (Burzynska et al., 2011). In the current study, MDD patients exhibited impaired WM performances with delayed reaction time, reduced accuracy, and reduced sensitivity index d' during the 2-back task. And the correlations between effective connectivity and psychological variables demonstrated that the stronger effective connectivity from right IPL to right dlPFC was associated with the poorer WM performances. As previous studies suggested that inefficient encoding might be partly responsible for WM deficit in MDD patients (Li et al., 2018; Murphy et al., 2019), our results provided further evidences that abnormal functional interactions within frontoparietal network could damage bottom-up stimuli encoding in MDD. In a word, our findings provided experimental clues to clarify the potential neuropathological mechanism of the abnormal effective connectivity within frontoparietal network in the WM deficits in MDD.

This study did not observe functional interaction within frontoparietal network at low load condition. Both the frontal and parietal regions are known to be involved in WM load-dependent network and executive control network (Höller-Wallscheid, Thier, Pomper, & Lindner, 2017; Tan et al., 2020). Increased complexity of n-back task requires more maintenance and manipulation of material and high amounts of cognitive processes, which is not necessary in a simpler condition (Gao et al., 2020). Therefore, the absence of abnormal functional interaction within frontoparietal network during the 0-back condition might suggest that MDD patients function normally on the low-level cognitive task, while the increased functional interactions within frontoparietal network during 2-back task might demonstrate that MDD patients have more difficulties to recruit these attentional control mechanisms in higher-order cognitive task.

Although previous studies investigated the functional connectivity between prefrontal and parietal cortex on the basis of temporal correlations, they could not indicate the direction and causal characteristic (Cao et al., 2020; Pan et al., 2020; Ye et al., 2012). Not only exploring the association between functional interaction and WM performances, depressive severity in MDD group, this study but also identified the direction of impaired parietal and prefrontal regions in MDD patients during WM task by integrating both data-driven (functional connectivity) and model-driven (effective connectivity) approaches.

Several potential limitations in this study should be mentioned. Firstly, we cannot entirely exclude the influence of medication. Although our major results did not change significantly after excluding the medicated patients, a sample with greater homogeneity (e.g., drug-naïve MDD patients) is still needed in future research to examine the replication of the findings in the present study. Secondly, different components of WM processes were not distinguished in our block-design WM task paradigm, while MDD patients showed different impairment characteristics during encoding, retrieval, and information manipulation (Wang et al., 2015). Future researches are needed to figure out the specific impaired subprocesses related to altered modulation in MDD. Thirdly, a relatively limited set of nodes in DCM analyses was included in the tested model space, which hindered to draw other conclusions, such as the contribution of connections among other brain regions to the impaired WM processing. Several previous DCM studies found altered effective connectivity within prefrontal-striatal, dlPFC-dorsal anterior cingulate cortex, posterior parietal cortex-anterior cingulate cortex in healthy individuals during the WM processing (Dima et al., 2014; Geiger et al., 2018; Ma et al., 2012), which seeds might be included in further studies to explore whether the results found in healthy individuals be present in MDD patients during WM processing. Finally, only task-related fMRI data were analyzed in this study, while multimodal-imaging investigations including both structural and functional MRI data might provide the better explanatory power of underlying neural bases of WM abilities in MDD, which should be conducted in the future.

5 | CONCLUSIONS

This study showed abnormal functional connectivity and effective connectivity among frontal and parietal regions during WM task in patients with MDD. Furthermore, impaired neural coupling strength from right IPL to right dlPFC indicated worse WM performances in high load WM task and severer depressive symptomatology. These findings provide new insights and evidences to elucidate the potential neuropathologic mechanism of impaired WM in patients with MDD.

CONFLICT OF INTEREST

All authors declared no potential conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Ethics committee of the Second Xiangya Hospital of Central South University.

PATIENT CONSENT STATEMENT

All participants were aware of the study's purpose and signed an informed consent form.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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