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Research Article

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Aberrant network topological structure of sensorimotor superficial white-matter system in major depressive disorder

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Abstract: White matter tracts play a pivotal role in transmitting sensory and motor information, facilitating interhemispheric communication and integrating different brain regions. Meanwhile, sensorimotor disturbance is a common symptom in patients with major depressive disorder (MDD). However, the role of aberrant sensorimotor white-matter system in MDD remains largely unknown. Herein, we investigated the topological structure alterations of white-matter morphological brain networks in 233 MDD patients versus 257 matched healthy controls (HC) from the DIRECT consortium. White-matter networks were derived from magnetic resonance imaging (MRI) data by combining voxel-based morphometry (VBM) and three-dimensional discrete wavelet transform (3D-DWT) approaches. Support vector machine (SVM) analysis was performed to discriminate MDD patients from HC. The results indicated that the network topological changes in node degree, node efficiency, and node betweenness were mainly located in the sensorimotor superficial white-matter system in MDD. Using network nodal topological properties as classification features, the SVM model could effectively distinguish MDD patients from HC. These findings provide new evidence to highlight the importance of the sensorimotor system in brain mechanisms underlying MDD from a new perspective of white-matter morphological network.

Key words: Major depressive disorder; Magnetic resonance imaging; White matter; Brain networks

1 Introduction

Major depressive disorder (MDD) is a common psychiatric condition characterized by a persistent low mood and/or decreased interest (anhedonia), accompanied by feelings of worthlessness, guilt and hopelessness, as well as unexplained physical anomalies (Malhi and Mann, 2018). Although no well-established brain mechanism has reasonably explained these symptoms and disease etiology, MDD patients have consistently been reported to have structural and functional alterations in brain areas and circuits (Zhang et al., 2018). With the development and applications of neuroimaging techniques and modern network theory (Petersen and Sporns, 2015), MDD is increasingly conceptualized as a brain network disorder (Bassett and Sporns, 2017). It has been further considered that MDD symptoms arise from network topological changes (Li et al., 2020). Previous researches have highlighted the disruption of topological properties of large-scale brain networks under the

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MDD condition based on global metrics such as global and local efficiencies, as well as nodal metrics including degree and betweenness (Li et al., 2021; Yang et al., 2021). For instance, a previous study reported a negative correlation between the characteristic path length and the rate of decrease in Hamilton Depression Scale (HAMD-24) scores after an 8-week antidepressant treatment in MDD (Zhang et al., 2021). Another study found alterations in the topological features of dynamic brain networks in MDD, specifically a significant decrease in the variability of clustering coefficient in the frontal cortex, parietal cortex and thalamus in individuals with MDD (Zhou et al., 2024). These brain network studies about altered topological properties somewhat broadened our insights into clinical diagnosis and treatment options.

The human brain is segmented into three tissue types: gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). WM is made up of bunches of myelinated axons of interconnecting neurons, forming distributed neural networks (Fields, 2010). Given that WM densely connects various GM regions and comprises approximately half the volume of the human brain, many previous researchers have focused on the topological changes of white-matter networks in normal and clinical populations, such as MDD patients (Sampaio and Johansen, 2017). Magnetic resonance imaging (MRI) is a noninvasive neuroimaging technique to map the anatomical structures, physiological functions and tissues of brain *in vivo*, while voxel-based morphometry (VBM), as a widely adaptable analytical method, has been used for measuring voxel-level volume/concentration of brain tissues such as GM and WM (Whitwell, 2009). Previous MRI-based brain network studies mainly focused on the organization patterns between GM regions (Power et al., 2011; Yeo et al., 2011). However, there is accumulating evidence that resting-state blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (rs-fMRI) signals can be reliably detected in white matter, and they dynamically fluctuate in a coordinated manner (Michael et al., 2017). For example, robust correlations have been observed between rs-fMRI signals from specific cortical GM regions and from segmented WM tracts (Wang et al., 2021).

Structural network connectivity can be mainly assessed via diffusion-weighted tractography to reconstruct axonal tracts between WM regions. Most white matter structural networks are based on diffusion tensor imaging (DTI), whereas DTI has been surrounded by several controversies, such as the presence of false-positive connections (Aydogan et al., 2018), sensitivity to noise during image acquisition, such as head motion (Baum et al., 2018), and uncertainty in quantifying long-distance connections (Schilling et al., 2019). Previous evidence from microscale biology and macroscopic brain imaging studies suggests that the morphological similarity of brain regions can, to some extent, infer structural connectivity (Meinertzhagen, 2018; Seidlitz et al., 2018). For example, a study tested whether large-scale structural reorganization in schizophrenia was related to normative network architecture, particularly to regional centrality/centrality and connectivity patterns, and suggested that schizophrenia was associated with widespread alterations in brain morphology and might be shaped by underlying connectome structures (Georgiadis et al., 2023). Based on these findings, it was hypothesized that axonal morphology can be applied to indirectly study structural connectivity between WM regions (Li et al., 2023). The morphology-informed analysis of structural connectivity may be particularly suited for WM regions due to their relatively homogeneous cellular composition, consisting of oligodendrocytes and astrocytes.

WM tracts are generally considered to play a pivotal role in transmitting sensory and motor information, facilitating interhemispheric communication and connecting various cortical regions (Wang et al., 2016). A growing body of research shows that MDD patients exhibit concurrent changes and a gradient in both low-level sensorimotor and higher-order cognitive processing (Xiao et al., 2023). On the other hand, it was previously indicated that a diverse range of sensorimotor stimulation could modulate depressive symptoms (Canbeyli, 2013). Some studies have also suggested that MDD might lead to disruptions in the sensory perception system, and conversely, these disruptions in auditory and visual functions might be preclinical signs of depression (Lu et al., 2020). A meta-analysis found reduced regional homogeneity (ReHo) of the sensorimotor network in MDD patients, which was thought to involve psychomotor retardation (Iwabuchi et al., 2015). Sensorimotor-related brain regions could complement brain mechanisms underlying MDD to some extent and might also serve as target areas in antidepressant therapy involving transcranial magnetic stimulation. Nevertheless, extant research in this domain is limited, prompting the need for a comprehensive understanding of the sensorimotor signal patterns in MDD.

In the present study, we investigated the topological properties of individual white-matter morphological networks derived from voxel-based morphometry (VBM) data using the three-dimensional discrete wavelet transform (3D-DWT) approach. Considering that sensorimotor changes have been shown to be significantly

involved in MDD, we hypothesized that aberrant network topological structure in the sensorimotor white-matter system would apparently mark MDD-related brain changes and might also discriminate MDD patients from normal controls. This study has great potential to highlight the clinical significance of the sensorimotor system in understanding the potential pathological mechanisms of MDD from the new perspective of white matter network.

2 Materials and methods

2.1 Participants

The dataset analyzed in the present study consisted of 233 MDD patients and 257 healthy controls (HC). Participants were drawn from a publicly available dataset contributed by the six study sites (Site 1, 2, 6, 7, 8 and 14) of the REST-meta-MDD project (Yan et al., 2019) from the DIRECT consortium (Chen et al., 2022). During screening, participants in the REST-meta-MDD consortium were first excluded if they: 1) had no information on gender, age and education; 2) were aged <18 years or >65 years; 3) had no information on the sub-item scores of the 17-item Hamilton Rating Scale for Depression (HAMD-17). Furthermore, we excluded stations with fewer than 10 MDD patients or 10 HC subjects to balance the subjects for optimizing the overall sample size and keeping extreme bias to a minimum. MDD patients were also excluded if they achieved a HAMD score of < 8 points. The primary approach for the diagnosis of MDD used operational diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders IV. The research protocols were carried out while following the recommendations of the Helsinki Declaration of Ethical Principles and approved by the local Institutional Review Boards (IRB) of each site. All study participants provided written informed IRB-approved consent before participating in the study procedures at their local institution.

Table 1 Demographic and clinical characteristics

Characteristics	MDD patients N = 233	HC N = 257	*t*/*χ2*	*p*
Age(years)	34.738 ± 11.170	33.883 ±11.295	0.842	0.400
Gender(male/female)	78/155	105/152	2.844	0.092
Education level(years)	12.223 ± 3.709	13.973 ± 3.526	-5.338	0.001
HAMD scores	23.537 ± 5.439	/	/	/

Abbreviation: HAMD, 17-item Hamilton Rating Scale for Depression; HC, healthy control; MDD, major depressive disorder.

2.2 White-matter network construction by three-dimensional discrete wavelet transform (3D-DWT)

The white matter morphological network was constructed by mapping inter-regional similarities based on regional morphology (i.e., WM volume) derived from structural MRI data. In this study, the nodes of the white matter morphological network were randomly generated anatomical nodes based on white matter volume, totalling 128 nodes. Connectivity was defined as the Pearson correlation coefficient of the wavelet feature vectors of regions of each node. The raw anatomical MRI data were pre-processed based on the standard procedure of VBM using DPABI software (http://www.rfmri.org/). The T1 images were first segmented into gray matter, white matter and cerebrospinal fluids in their original space, and the white matter images were subsequently modulated and spatially normalized using the DARTEL toolbox (Ashburner, 2007). The normalized images were modulated by multiplying the Jacobean determinants derived from previous DARTEL spatial normalization.

Wavelet transformation is a multiscale analysis method that transforms the energy of a signal into hierarchically organized levels of resolution, allowing the capture of both local and global features of anatomical MRI datasets. In this study, three-dimensional discrete wavelet transformation (3D-DWT) was applied to the

voxel-wise white matter volume using the waverec3 function in MATLAB (Wang et al., 2022). Each voxel was decomposed into three different levels, and each level was further divided into high-pass and low-pass components. As a result, six (3×2) wavelet features were generated based on the volume of each voxel. An average white-matter structural mask across all participants was segmented into 128 contiguous anatomical regions (128 network nodes) across the whole brain using the region-growing method reported by previous studies (Zalesky et al., 2010). The average wavelet feature vector of all voxels within each node was defined as the regional wavelet feature vector. The white matter morphological similarity matrix (128×128) of each subject was obtained using the Pearson correlation coefficient between each pair of regional wavelet feature vectors, and then normalized using Fisher's r to z transformation. Follow-up analysis of network topological properties was performed based on the weighted WM similarity matrix. A schematic analysis of individual white-matter morphological networks is shown in Fig. 1.

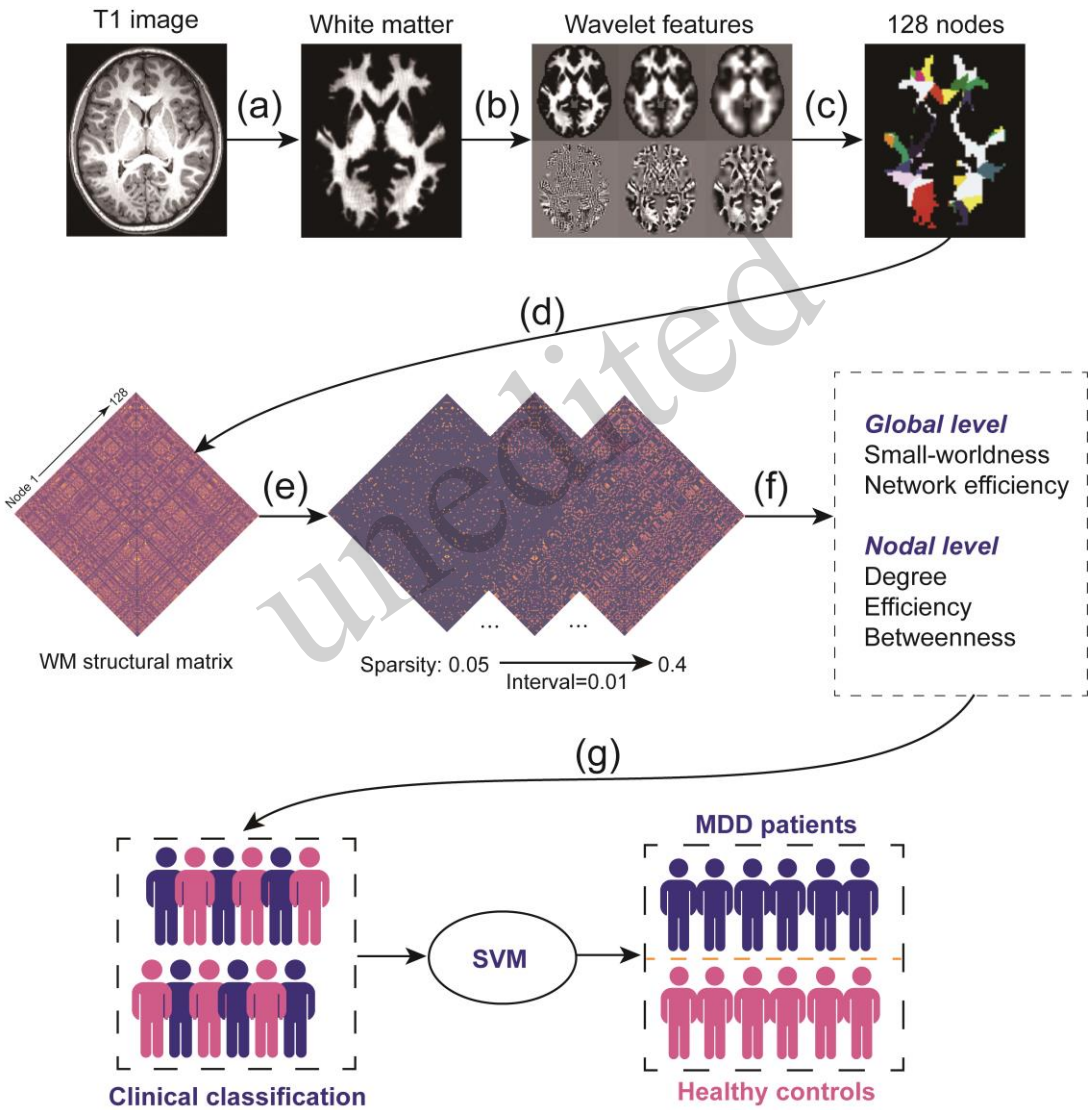

Fig. 1 Flowchart for the construction and analysis of individual white-matter morphological networks.
(a) For each subject, voxel-based morphology (VBM) transform was performed on the spatially normalized and modulated T1 weighted white matter images. (b) 3D wavelet transform was performed on the individual VBM volume. (c) The group-level WM mask was randomly separated into 128 anatomical nodes with an approximately identical size. The white matter was assigned to 128 nodes. (d) Interregional morphological similarity was computed based on the correlation coefficients of the node's wavelet features. (e) The WM white-matter morphological networks were constructed across a series of sparsities from 0.05–0.4 (interval = 0.01). (f) The AUC values of topological properties (i.e., small-world topology and nodal topological properties) were then evaluated across a series of sparsity values. (g) The support vector machine model was used to classify MDD and HC. AUC, area

under the curve; GM, gray matter; HC, healthy control; MDD, major depressive disorder; WM, white matter; SVM, support vector machine.

2.3 Graph theory analysis of white-matter networks

The graph theory analysis of WM networks was performed using GRETNA software (Wang et al., 2015). We calculated the network topological properties over a range of network sparsity thresholds (from 5% to 40%, with 1% step size) for each individual weighted matrix. The global properties included clustering coefficient (C_p), characteristic path length (L_p), normalized clustering coefficient (γ), normalized characteristic path length (λ), global efficiency (E_{glob}), local efficiency (E_{loc}), and small-worldness (σ). The nodal properties included node efficiency, node degree, and node betweenness. Some global properties were further normalized using the corresponding average of 100 matched random networks, generated by a topological rewiring algorithm to maintain the same degree distribution as the real networks (Maslov and Sneppen, 2002). Small-world WM networks have global properties ($\gamma > 1$ and $\lambda \approx 1$, or $\delta = \gamma / \lambda > 1$) that indicate a relatively higher local interconnectivity and an approximately equivalent shortest path length compared with random networks (Liao et al., 2017).

The small-worldness of a complex network is described by its C_p and L_p values, where C_p refers to the number of edges between a node's nearest neighbours and indexes network segregation, and L_p represents the average shortest path length between all pairs of nodes in the network, which reflects the degree of network integration (Li et al., 2021). Global efficiency in the brain network is defined as "a measure of the overall capacity for parallel information transfer and integrated processing" (Bullmore and Sporns, 2012). These topological properties are known to be interrelated, with each providing a different viewpoint from which the major features of the large-scale architecture can be discerned (Zhang et al., 2011). The three nodal metrics selected in this study are among the most commonly utilized indicators in previous research. Nodal topological properties typically measure local information transfer efficiency, and alterations in nodal efficiency are considered to be associated with cognitive inhibitory deficits and depressive states (Li et al., 2021). To examine the distribution of nodes and between-group differences in nodal topological properties at the network level, we mapped the nodes with between-group differences ($p < 0.05$, FDR corrected) onto the defined 12 white matter networks. The ComBat harmonization models were implemented to remove the confounding effects introduced by the site effects, with age, gender and diagnosis as covariates (Fortin et al., 2018).

2.4 Statistical analysis

The two-sample t-test was applied to analyze the between-group differences of demographic and clinical data. The chi-square test was used to measure gender differences between the MDD and HC groups. The global and nodal topological properties were compared between MDD and HC using non-parametric Mann-Whitney U tests, with age, gender, education, and head movement as covariates. Head movement, quantified using framewise displacement (FD) derived from the subjects' fMRI scans, was considered in light of prior research demonstrating the potential impact of in-scanner head motion on morphometric measures (Alexander et al., 2016; Pardoe and Martin, 2022). The threshold of statistical significance was set at 0.05, corrected for multiple comparisons with a false-discovery rate method ($p < 0.05$, FDR corrected). We mapped network nodes with significant differences to 12 white matter networks according to previous high-quality research (Peer et al., 2017) (see Table 2). The Pearson correlation coefficients between the topological properties and HAMD scores were calculated in the MDD group. The false discovery rate (FDR) correction was applied separately to between-group comparisons of global topological properties, local topological properties, and network-level topological properties, with a threshold set at $p < 0.05$ for each type. Finally, we used support vector machine (SVM) classification models based on the area under the curve (AUC) values of global and nodal topological properties to distinguish between MDD and HC, and applied 5-fold cross-validation to the models.

Table 2 The white matter networks

Network label	Network name
1	Cingulum and associated tracts
2	Uncinate and middle temporal lobe tracts
3	Sensorimotor superficial white-matter system
4	Forceps minor system
5	Superior longitudinal fasciculus system
6	Visual superficial white-matter system
7	Inferior longitudinal fasciculus system
8	Inferior corticospinal tract
9	Posterior cerebellar tracts
10	Dorsal frontoparietal tracts
11	Deep frontal white matter
12	Ventral frontoparietal tracts

2.5 Classification model based on the topological properties of WM morphological network

Aiming to study the clinical application of the topological properties of the constructed white matter structural network, we used a support vector machine (SVM) model with a linear kernel function in Python's scikit-learn (https://scikit-learn.org/) to distinguish MDD patients from HC. The AUC values of global topological attributes (including γ, λ, σ, C_p, L_p, global efficiency, and local efficiency) and nodal topological attributes (including node degree, node efficiency, and node betweenness of 128 nodes) of each patient were used as classification features. We finally created two classification models, that is, the support vector machine classification model based on global topological properties and that based on nodal topological properties. We employed five-fold cross-validation to the SVM classification model, with the outputs of accuracy and the AUC value of the ROC curve for each fold as evaluation metrics for the classification model. Finally, to illustrate the ultimate classification performance, we computed the average AUC value and accuracy for each model.

3 Results

3.1 Between-group differences of network global topological properties

Fig. 2A and B present the comparison results of AUC values of global network properties. Compared with HC, MDD patients showed a statistically significant increase in σ (Mann-Whitney U test, Z = 2.60, p = 0.009, FDR-corrected) and decrease in L_p (Mann-Whitney U test, Z = -2.67, p = 0.007, FDR-corrected). The other global network properties(λ, γ, C_p, E_{glob} and E_{loc}) showed no significant between-group differences (p > 0.05). No significant correlations were found between two indicators (σ and L_p) and the HAMD scores (p > 0.05).

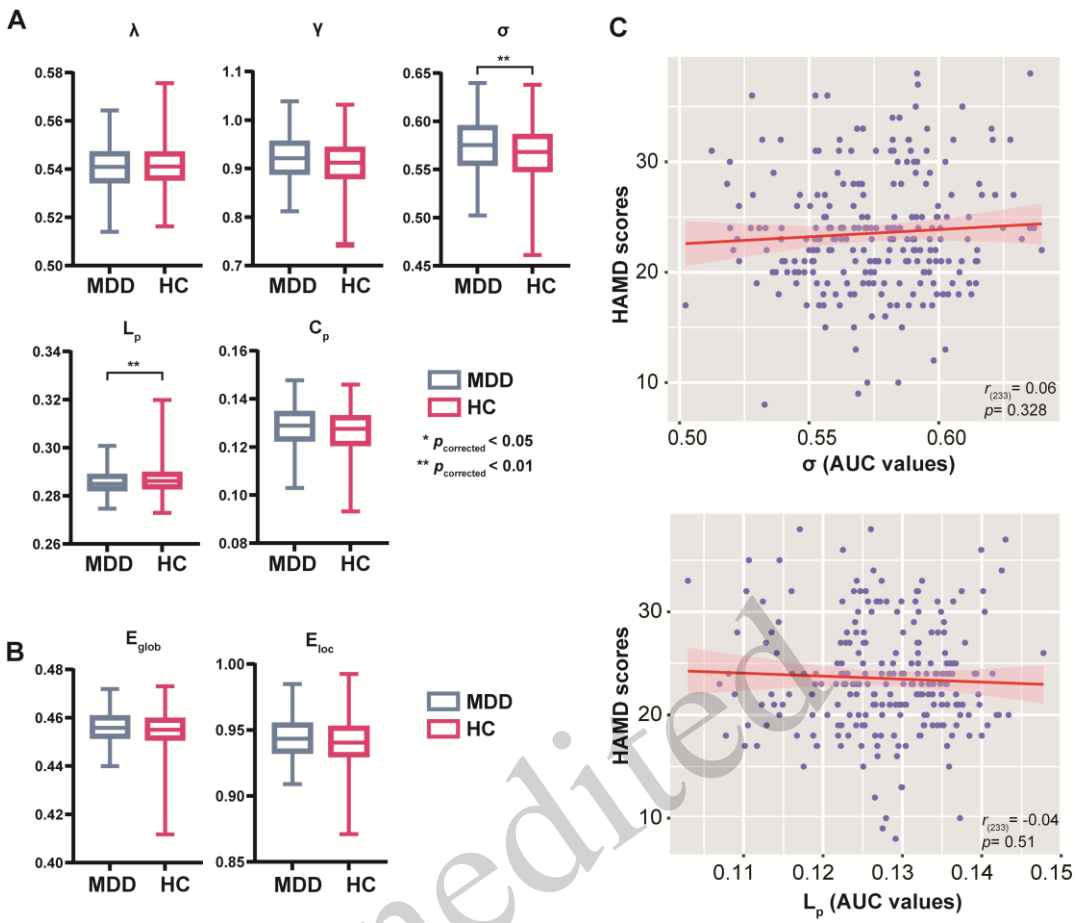

Fig. 2 Between-group differences of network global topological properties.

C_p, clustering coefficient; L_p, characteristic path length; γ, normalized clustering coefficient; λ, normalized characteristic path length; E_{glob}, global efficiency; E_{loc}, local efficiency; σ, small-worldness; AUC, area under curve; HAMD, 17-item Hamilton Depression Scale.

3.2 Between-group differences of network nodal topological properties

As shown in the left half of Fig. 3, MDD patients exhibited 30, 37 and 18 network nodes with significant differences (p < 0.05, FDR corrected) in node degree, node efficiency and node betweenness compared to HC, respectively. To examine the distribution of nodes on each network, we separately summarized the number of nodes with significant differences in each of the 12 networks, shown in the right half of Fig. 3. Network 3, described as the sensorimotor superficial white-matter system (see Table 2), had the maximum number of nodes with between-group differences (see the right half of Fig. 3; node degree: 9; node efficiency: 10; node betweenness: 7). There were no significant correlations found between these indicators and the HAMD scores (p > 0.05).

As shown in Fig. 4, MDD patients showed statistically significant increase in the AUC values of node degree (Z = 4.48, p < 0.001, FDR corrected) and node efficiency (Z = 3.76, p = 0.002, FDR corrected), and decrease in the AUC values of node betweenness (Z = -3.12, p = 0.011, FDR corrected), mainly in the sensorimotor superficial white-matter system (Network 3) compared to HC. Besides, we found that MDD patients exhibited significant decrease in the AUC values of node degree (Z = -3.80, p < 0.001, FDR corrected) and node betweenness (Z = -3.22, p = 0.015, FDR corrected) in Network 1, of node efficiency (Z = -2.76, p = 0.035, FDR corrected) in Network 2, and of node betweenness (Z = -2.89, p = 0.015, FDR corrected) in Network 7.

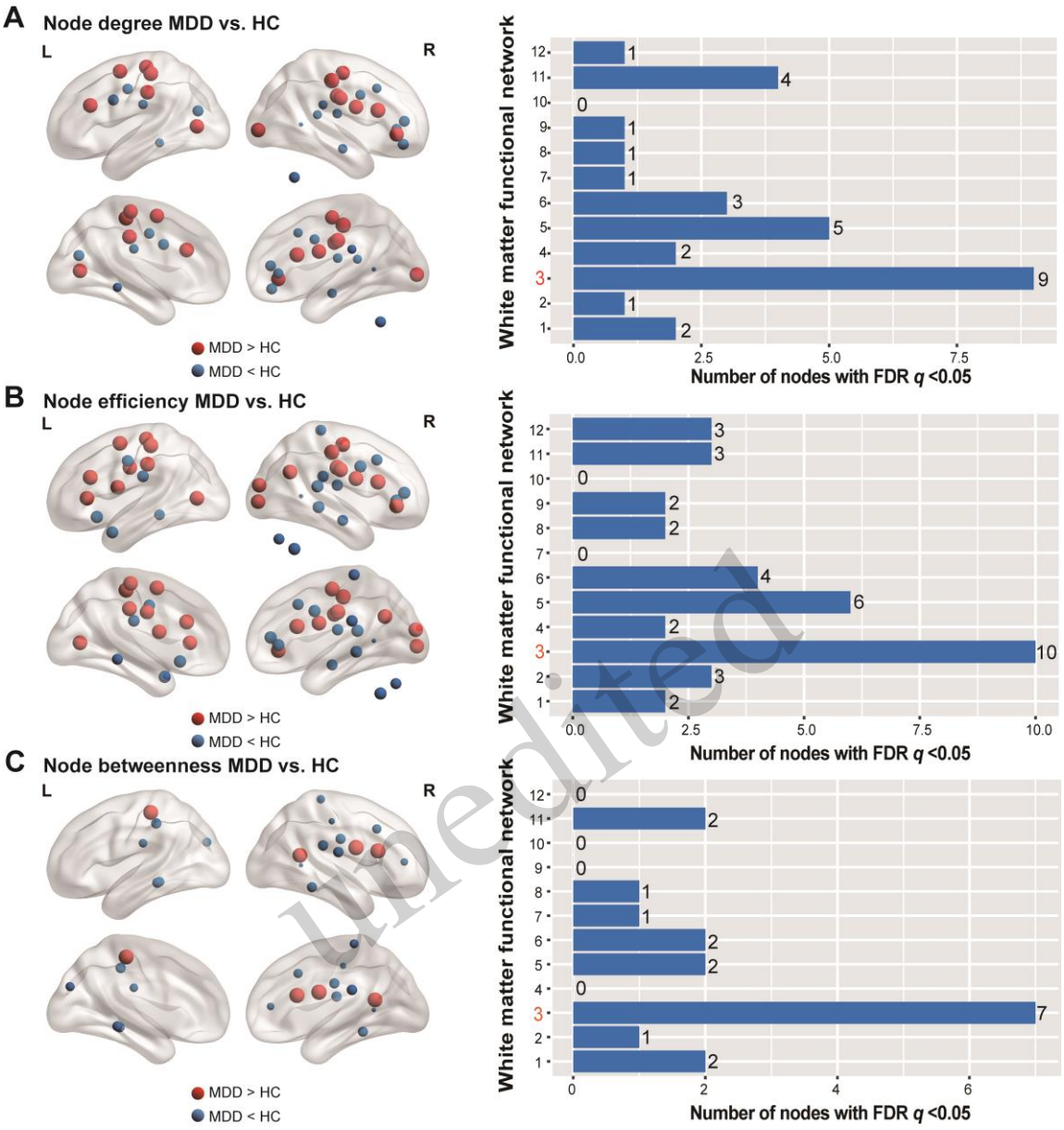

Fig. 3 Between-group differences of network nodal topological properties.

The balls indicate significant between-group differences in the nodal topological properties (p<0.05), where red and blue balls denote increase and decrease in MDD compared to HC, respectively. The sphere size represents the significance of the difference (the Z value of the statistical test).

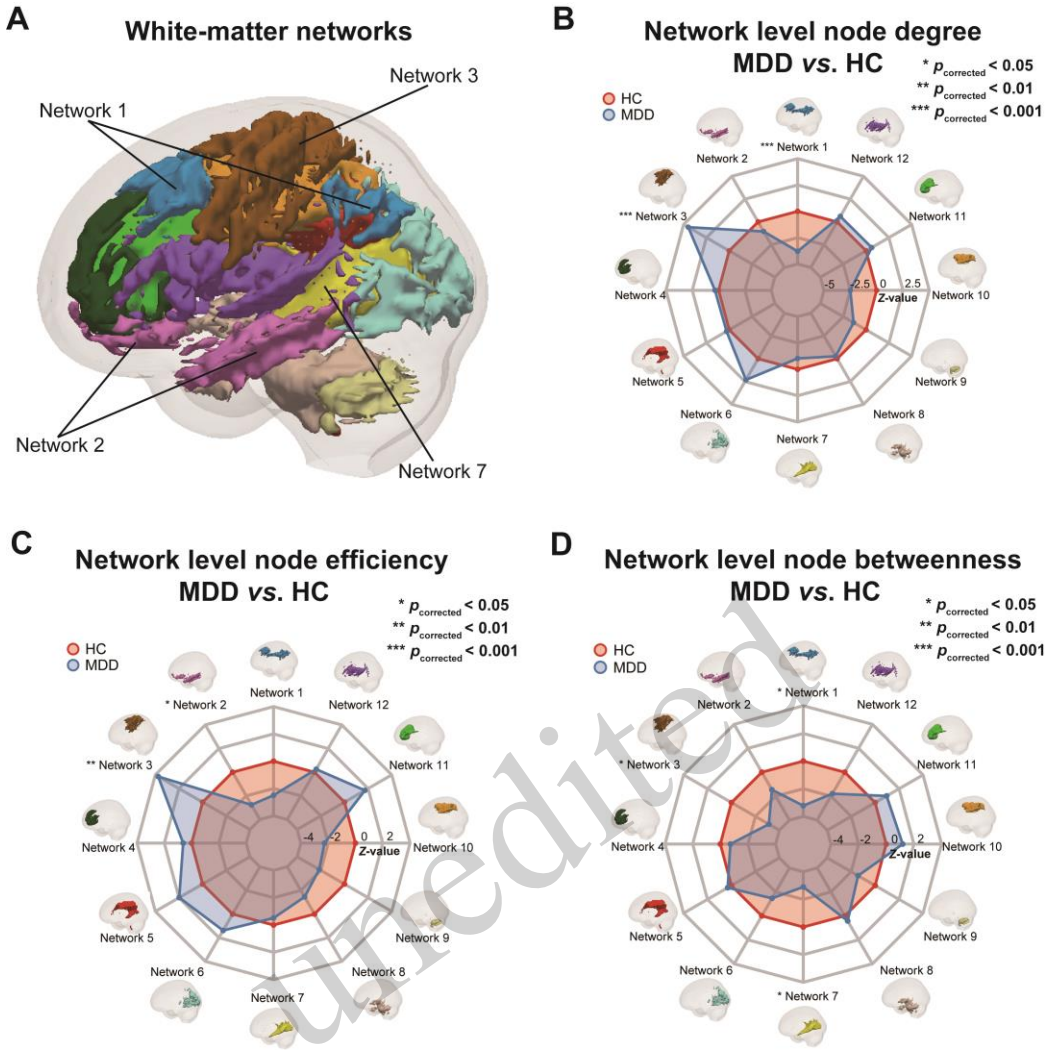

Fig. 4 Between-group comparison of nodal topologies in 12 white matter networks.
The white-matter networks were defined by Peer's 12 white-matter network parcellation atlas.

3.3 Classification results based on the topological properties of white-matter networks

As shown in Fig. 5, the average accuracy of the classification model based on global topological properties was 56.7% and its classification AUC value was 61.1% (sensitivity = 50% and specificity = 64%), while the average accuracy on nodal topological properties was 73% and its classification AUC value was 80.3% (sensitivity = 72%, specificity = 75%).

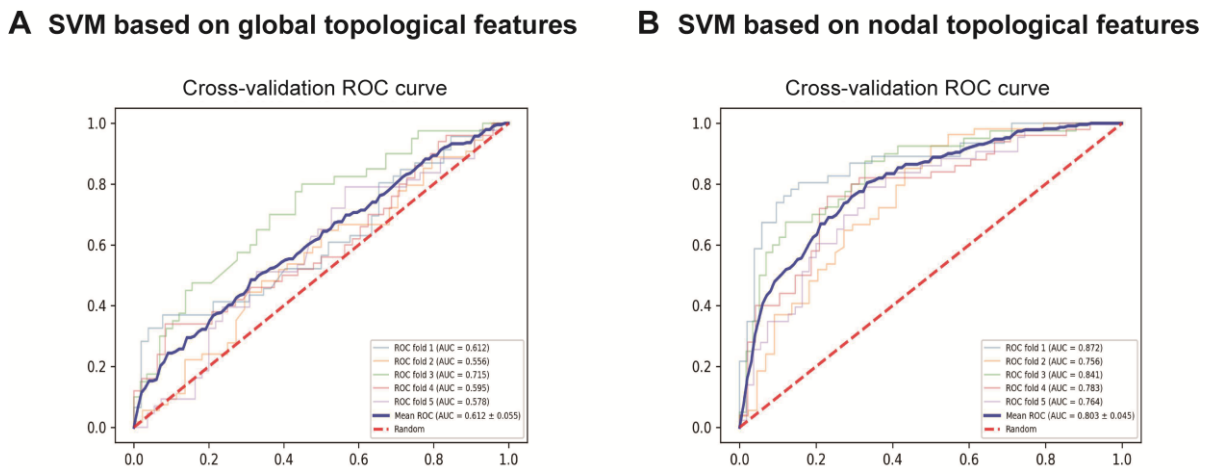

Fig. 5 Performance evaluation of support vector machine classification.
AUC, area under the curve; ROC, receiver operator characteristic.

4 Discussion

To the best of our knowledge, this is the first study to map MDD-related individual-level brain WM network changes by using a combination of a wavelet transform method and structural MRI-based brain morphological data. We found that MDD-related topological structure changes of the WM network primarily occurred in the sensorimotor superficial white-matter system. Interregional morphological similarity was first computed to construct a WM network for each participant using 3D wavelet transform based on the white matter volume derived from VBM data. Subsequently, the graph theory method was used to characterize the network global and nodal topological abnormalities in MDD. A support vector machine model based on the nodal topological properties achieved a classification accuracy of 73%, which effectively differentiated MDD patients from HC. These results provide new evidence highlighting the clinical significance of the sensorimotor system and enhancing our understanding of the potential pathological mechanisms of MDD from the new perspective of white matter network.

Our findings demonstrated the distinctive characteristics of morphological similarity or structure connectivity of white-matter brain networks. These included reduced characteristic path length and increased small-worldness in MDD patients. The observed decrease in L_p in MDD patients suggested an increased integration capacity within the brain, indicating unusual information transmission. This finding aligns with a previous study reporting similar characteristics in the topological properties of functional brain networks in MDD, which indicated abnormally low L_p and higher overall efficiency (inversely related to L_p). This was explained as a less regular organized or randomization structure within the white matter network (Zhang et al., 2011). Our result on the abnormal small-world properties in MDD is consistent with the previous findings for white matter functional networks (Li et al., 2020; Yang et al., 2021). This structural basis of aberrant white matter in MDD might be an important factor underlying the wiring patterns of brain networks.

The current study presents new data on the alterations in WM networks associated with MDD. Specifically, the observed elevation in the node degree and node efficiency of the sensorimotor superficial white-matter system in MDD suggests a heightened level of local interconnectedness and information processing within these regions (Petrella, 2011). This amplified local connectivity might signify a compensatory mechanism or an adaptive response to mitigate disturbances in sensorimotor functions associated with MDD (Luscher et al., 2011). Conversely, the notable reduction in node betweenness within the sensorimotor superficial white-matter system implies a reduced capacity to act as key intermediaries in information transfer across brain networks (Korgaonkar et al., 2014). This decline in the pivotal role of the white-matter system might indicate a disrupted flow of information or impaired integration of sensorimotor-related WM tracts in MDD. Significant correlations have been reported between the abnormal topological structure of the sensorimotor white matter system and

some cognitive scores in MDD (Wang et al., 2022). These topological alterations also highlight the intricate network connectivity changes in white matter network topologies associated with MDD.

Understanding how the structural connectivity pattern supports and shapes brain function is a fundamental question in systems neuroscience (Honey et al., 2010). The morphological WM network is optimally organized to support efficient information transmission and processing. Specifically, WM tracts play a crucial role in transmitting sensory and motor information, mediating interhemispheric communication, and connecting various cortical regions (Filley, 1998). It has been suggested that the loss of WM integrity in the frontal lobe might exist across various elder populations and that WM lesions might disrupt neural circuits involved in emotion regulation, involving the neuropathology of MDD (Ma et al., 2007). Our findings suggest that the abnormalities in cognitive control and emotional regulation observed in MDD patients might partly result from shortened information transmission and processing capacity in the sensorimotor network. This may be because the sensorimotor superficial white-matter system interconnects the default mode, posterior attention, ventral attention, and frontoparietal control networks, suggesting the mediating role of white matter networks between these gray matter network regions across varying distances (Peer et al., 2017). The latter study categorized the organization of white matter networks into three tiers, with the superficial white matter network significantly correlated with gray matter networks while the deep network showing relatively less dependence on gray matter networks. Among these, the sensorimotor superficial white-matter system is a symmetric white matter network distributed throughout the entire brain. This further supports the previous notion that superficial white matter networks may indirectly interact with gray matter networks, whereas mid-level and deep white matter networks are more likely to communicate directly through axonal interactions (Fan et al., 2020). We tentatively propose that structural topological abnormalities in sensorimotor superficial white matter systems might involve the disruption of connections to regions highly associated with cognitive functions, which warrants further investigation.

Using SVM classification models, we further explored whether the topological properties of white matter network could serve as potential biomarkers for the clinical identification of MDD patients. Our results showed with 73% accuracy that the nodal topological properties of white matter networks could effectively distinguish MDD patients from healthy controls. Previous studies have distinguished MDD and HC with accuracies of 66% (Ramasubbu et al., 2016), 63.7% (Shi et al., 2021), and 73.3% (Nakano et al., 2020) while using the SVM classification model. Another study also found that the small-world topological properties of the white matter functional network can distinguish between unmedicated MDD patients and healthy control subjects, with an accuracy rate of 76% (Li et al., 2020). Considering the above accuracy rates, the accuracy rate of 73% and AUC value of 80.3% in this study essentially constitutes a good classification performance and can guide potential clinical applications. In this way, our findings provide supplementary evidence about morphological networks underlying MDD.

The present study has several limitations that need to be addressed. Firstly, previous MDD studies traditionally focused on aberrations in higher-order brain functions, including emotion regulation and attention control. Our findings based on the white matter network predominantly centers on the abnormalities of primary sensorimotor functions, providing new insights into the pathophysiology of MDD. Meanwhile, further investigating the relationship between white matter networks and emotional functions is a meaningful direction. Secondly, common research approaches to characterize white matter networks still remain insufficient. Beyond the morphological 3D-wavelet transform method utilized in the present study, there is a further need for the development and refinement of novel research methodologies pertaining to white matter.

5 Conclusions

In the present study, we detected abnormalities in the sensorimotor superficial white-matter system of MDD patients, which might serve as new neurobiological markers for this disorder. Moreover, we successfully achieved a good performance based on nodal topological properties of the WM network in distinguishing MDD patients from healthy controls, providing a valuable reference for clinical research.

Data availability statement

The dataset of participants is available through a reasonable request to the Rest-meta-MDD consortium

(http://rfmri.org/REST-meta-MDD).

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Author contributions

Peng WANG and Yang XIAO designed the research. Peng WANG analyzed data. Yanling BAI drafted the original manuscript. Yanling Bai and Peng WANG edited and revised manuscript; Yuhong ZHENG, Li SUN, Jinhui WANG and Shao-Wei XUE reviewed and revised the manuscript. All authors read and approved the final manuscript and, therefore, had full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Peng WANG, Yanling BAI, Yang XIAO, Yuhong ZHENG, Li SUN, Jinhui WANG and Shao-Wei XUE declare that they have no conflict of interest declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

References

Alexander A, Clasen L, Stockman M, et al., 2016. Subtle in-scanner motion biases automated measurement of brain anatomy from in vivo mri. *Hum Brain Mapp*, 37(7), 2385-2397. https://doi.org/10.1002/hbm.23180

Ashburner J. 2007. A fast diffeomorphic image registration algorithm. *NeuroImage, 38*(1), 95-113. https://doi.org/10.1016/j.neuroimage.2007.07.007

Aydogan DB, Jacobs R, Dulawa S, et al., 2018. When tractography meets tracer injections: A systematic study of trends and variation sources of diffusion-based connectivity. *Brain Struct Funct*, 223(6), 2841-2858. https://doi.org/10.1007/s00429-018-1663-8

Bassett DS, Sporns O. 2017. Network neuroscience. *Nat Neurosci*, 20(3), 353-364. https://doi.org/10.1038/nn.4502

Baum GL, Roalf DR, Cook PA, et al., 2018. The impact of in-scanner head motion on structural connectivity derived from diffusion mri. *Neuroimage*, 173, 275-286. https://doi.org/10.1016/j.neuroimage.2018.02.041

Bullmore E, Sporns O. 2012. The economy of brain network organization. *Nat Rev Neurosci*, 13(5), 336-349. https://doi.org/10.1038/nrn3214

Canbeyli R, 2022. Sensorimotor modulation of mood and depression: in search of an optimal mode of stimulation. *Front Hum Neurosci*, 7:428. https://doi.org/10.3389/fnhum.2013.00428.

Chen X, Lu B, Li HX, et al., 2022. The direct consortium and the rest-meta-mdd project: Towards neuroimaging biomarkers of major depressive disorder. *Psychoradiology*, 2(1), 32-42. https://doi.org/10.1093/psyrad/kkac005

Fan YS, Li Z, Duan X, et al., 2020. Impaired interactions among white-matter functional networks in antipsychotic-naive first-episode schizophrenia. *Hum Brain Mapp*, 41(1), 230-240. https://doi.org/10.1002/hbm.24801

Fields RD. 2010. Neuroscience. Change in the brain's white matter. *Science*, 330(6005), 768-769. https://doi.org/10.1126/science.1199139

Filley CM. 1998. The behavioral neurology of cerebral white matter. *Neurology*, 50(6), 1535-1540. https://doi.org/10.1212/WNL.50.6.1535

Fortin JP, Cullen N, Sheline YI, et al., 2018. Harmonization of cortical thickness measurements across scanners and sites. *NeuroImage*, 167, 104-120. https://doi.org/10.1016/j.neuroimage.2017.11.024

Georgiadis F, Larivière S, Glahn D, et al., 2023. Connectome architecture shapes large-scale cortical reorganization in schizophrenia: A worldwide enigma study. 2023.2002.2012.527904. https://doi.org/10.1101/2023.02.12.527904

Honey CJ, Thivierge JP, Sporns O. 2010. Can structure predict function in the human brain? *NeuroImage, 52*(3), 766-776. https://doi.org/10.1016/j.neuroimage.2010.01.071

Iwabuchi SJ, Krishnadas R, Li C, et al., 2015. Localized connectivity in depression: A meta-analysis of resting state functional imaging studies. *Neurosci Biobehav Rev*, 51, 77-86.

https://doi.org/10.1016/j.neubiorev.2015.01.006
Korgaonkar MS, Fornito A, Williams LM, et al., 2014. Abnormal structural networks characterize major depressive disorder: A connectome analysis. *Biol Psychiatry,* 76(7), 567-574.
https://doi.org/10.1016/j.biopsych.2014.02.018
Li H, Yang J, Yin L, et al., 2021. Alteration of single-subject gray matter networks in major depressed patients with suicidality. *J Magn Reson Imaging,* 54(1), 215-224.
https://doi.org/10.1002/jmri.27499
Li J, Chen H, Fan F, et al., 2020. White-matter functional topology: A neuromarker for classification and prediction in unmedicated depression. *Transl Psychiat,* 10(1), 365.
https://doi.org/10.1038/s41398-020-01053-4
Li J, Li Z, Yang Y, et al., 2023. Morphological brain networks of white matter: Mapping, evaluation, characterization and application. 2023.2006.2002.543370.
https://doi.org/10.1101/2023.06.02.543370
Liao X, Vasilakos AV, He Y. 2017. Small-world human brain networks: Perspectives and challenges. *Neurosci Biobehav Rev,* 77, 286-300.
https://doi.org/10.1016/j.neubiorev.2017.03.018
Lu F, Cui Q, Huang X, et al., 2020. Anomalous intrinsic connectivity within and between visual and auditory networks in major depressive disorder. *Prog Neuro-Psychoph,* 100, 109889.
https://doi.org/10.1016/j.pnpbp.2020.109889
Luscher B, Shen Q, Sahir N. 2011. The gabaergic deficit hypothesis of major depressive disorder. *Mol Psychiatry, 16*(4), 383-406.
https://doi.org/10.1038/mp.2010.120
Ma N, Li L, Shu N, et al., 2007. White matter abnormalities in first-episode, treatment-naive young adults with major depressive disorder. *Am J Psychiatry, 164*(5), 823-826.
https://doi.org/10.1176/ajp.2007.164.5.823
Malhi GS, Mann JJ. 2018. Depression. *Lancet, 392*(10161), 2299-2312.
https://doi.org/10.1016/s0140-6736(18)31948-2
Maslov S, Sneppen K. 2002. Specificity and stability in topology of protein networks. *Science, 296*(5569), 910-913.
https://doi.org/10.1126/science.1065103
Meinertzhagen IA. 2018. Of what use is connectomics? A personal perspective on the drosophila connectome. *J Exp Biol,* 221(10).
https://doi.org/10.1242/jeb.164954
Michael P, Mor N, Atira SB, et al., 2017. Evidence for Functional Networks within the Human Brain's White Matter. *J Neurosci, 37*(27), 6394.
https://doi.org/10.1523/JNEUROSCI.3872-16.2017
Nakano T, Takamura M, Ichikawa N, et al., 2020. Enhancing multi-center generalization of machine learning-based depression diagnosis from resting-state fmri. *Front Psychiatry* ,11, 489914.
https://doi.org/10.3389/fpsyt.2020.00400
Pardoe HR, Martin SP. 2022. In-scanner head motion and structural covariance networks. *Hum Brain Mapp,* 43(14), 4335-4346.
https://doi.org/10.1002/hbm.25957
Peer M, Nitzan M, Bick AS, et al., 2017. Evidence for functional networks within the human brain's white matter. *J Neurosci,* 37(27), 6394-6407.
https://doi.org/10.1523/JNEUROSCI.3872-16.2017
Petersen SE, Sporns O. 2015. Brain networks and cognitive architectures. *Neuron,* 88(1), 207-219.
https://doi.org/10.1016/j.neuron.2015.09.027
Petrella JR. 2011. Use of graph theory to evaluate brain networks: A clinical tool for a small world? *Radiology,* 259(2), 317-320.
https://doi.org/10.1148/radiol.11110380
Power JD, Cohen AL, Nelson SM, et al., 2011. Functional network organization of the human brain. *Neuron,* 72(4), 665-678.
https://doi.org/10.1016/j.neuron.2011.09.006
Ramasubbu R, Brown MRG, Cortese F, et al., 2016. Accuracy of automated classification of major depressive disorder as a function of symptom severity. *NeuroImage: Clinical,* 12, 320-331.
https://doi.org/10.1016/j.nicl.2016.07.012
Sampaio BC, Johansen BH. 2017. White matter plasticity in the adult brain. *Neuron,* 96(6), 1239-1251.
https://doi.org/10.1016/j.neuron.2017.11.026
Schilling KG, Gao Y, Stepniewska I, et al., 2019. Anatomical accuracy of standard-practice tractography algorithms in the motor system - a histological validation in the squirrel monkey brain. *Magnetic Resonance Imaging,* 55, 7-25.
https://doi.org/10.1016/j.mri.2018.09.004
Seidlitz J, Váša F, Shinn M, et al., 2018. Morphometric similarity networks detect microscale cortical organization and predict inter-individual cognitive variation. *Neuron,* 97(1), 231-247.e237.
https://doi.org/10.1016/j.neuron.2017.11.039
Shi Y, Zhang L, Wang Z, et al., 2021. Multivariate machine learning analyses in identification of major depressive disorder using resting-state functional connectivity: A multicentral study. *ACS Chemical Neuroscience,* 12(15), 2878-2886.
https://doi.org/10.1021/acschemneuro.1c00256
Wang J, Wang X, Xia M, et al., 2015. Gretna: A graph theoretical network analysis toolbox for imaging connectomics. *Front Hum*

Neurosci, 9, 386.
https://doi.org/10.3389/fnhum.2015.00386

Wang P, Wang J, Michael A, et al., 2021. White matter functional connectivity in resting-state fmri: Robustness, reliability, and relationships to gray matter. *Cereb Cortex*, 32(8), 1547-1559.
https://doi.org/10.1093/cercor/bhab181

Wang XH, Zhao B, Li L. 2022. Mapping white matter structural covariance connectivity for single subject using wavelet transform with t1-weighted anatomical brain mri. *Front Neurosci*, 16, 1038514.
https://doi.org/10.3389/fnins.2022.1038514

Wang Y, Liu G, Hong D, et al., 2016. White matter injury in ischemic stroke. *Prog Neurobiol*, 141, 45-60.
https://doi.org/10.1016/j.pneurobio.2016.04.005

Whitwell JL. 2009. Voxel-based morphometry: An automated technique for assessing structural changes in the brain. *J Neurosci*, 29(31), 9661-9664.
https://doi.org/10.1523/jneurosci.2160-09.2009

Xiao Y, Zhao L, Zang X, et al., 2023. Compressed primary-to-transmodal gradient is accompanied with subcortical alterations and linked to neurotransmitters and cellular signatures in major depressive disorder. *Hum Brain Mapp*, 44(17), 5919-5935.
https://doi.org/10.1002/hbm.26485

Yan CG, Chen X, Li L, et al., 2019. Reduced default mode network functional connectivity in patients with recurrent major depressive disorder. *PNAS*, 116(18), 9078-9083.
https://doi.org/10.1073/pnas.1900390116

Yang H, Chen X, Chen ZB, et al., 2021. Disrupted intrinsic functional brain topology in patients with major depressive disorder. *Mol Psychiatry*, 26(12), 7363-7371.
https://doi.org/10.1038/s41380-021-01247-2

Yeo BT, Krienen FM, Sepulcre J, et al., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*, 106(3), 1125-1165.
https://doi.org/10.1152/jn.00338.2011

Zalesky A, Fornito A, Harding IH, et al., 2010. Whole-brain anatomical networks: Does the choice of nodes matter? *Neuroimage*, 50(3), 970-983.
https://doi.org/10.1016/j.neuroimage.2009.12.027

Zhang FF, Peng W, Sweeney JA, et al., 2018. Brain structure alterations in depression: Psychoradiological evidence. *Cns Neurosci Ther*, 24(11), 994-1003.
https://doi.org/10.1111/cns.12835

Zhang Y, Liu X, Hou Z, et al., 2021. Global topology alteration of the brain functional network affects the 8-week antidepressant response in major depressive disorder. *J Affect Disord*, 294, 491-496.
https://doi.org/10.1016/j.jad.2021.07.078

Zhang Z, Liao W, Chen H, et al., 2011. Altered functional–structural coupling of large-scale brain networks in idiopathic generalized epilepsy. *Brain*, 134(10), 2912-2928.
https://doi.org/10.1093/brain/awr223

Zhou Y, Zhu Y, Ye H, et al., 2024. Abnormal changes of dynamic topological characteristics in patients with major depressive disorder. *J Affect Disord*, 345, 349-357.
https://doi.org/10.1016/j.jad.2023.10.143