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Dysfunctional large-scale brain networks in drug-naïve depersonalization-derealization disorder patients

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Abstract

Background Depersonalization-Derealization Disorder (DPRD) presents challenges in understanding its neurobiological underpinnings. Several neuroimaging studies have revealed altered brain function and structure in DPRD. However, the knowledge about large-scale dysfunctional brain networks in DPRD remains unknown.

Methods A total of 47 drug-naïve DPRD patients and 49 healthy controls (HCs) were recruited and underwent resting-state functional scanning. After constructing large-scale brain networks, we calculated within-and between-network functional connectivity (FC) using the Schaefer and Tian atlas. The Support Vector Machine (SVM) model was employed to classify DPRD patients and provide features for DPRD patients concerning the dysfunctional large-scale brain networks. Finally, the correlation analysis was performed between altered functional connectivity of large-scale brain networks and scores of clinical assessments in DPRD patients.

Results Compared to HCs, we found significantly decreased FCs, within-networks across four brain networks and between-networks involving 18 pairs of brain networks in DPRD patients. Moreover, our results revealed a satisfactory classification accuracy (80%) of these decreased FCs for correctly identifying DPRD patients. Notably, a significant negative correlation was observed between the 'Self' factor of the CDS and the FC within the somatosensory-motor network.

Conclusion Overall, disrupted FC of large-scale brain networks may contribute to understanding neurobiological underpinnings in DPRD. Our findings may provide potential targets for therapeutic interventions.

Keywords Depersonalization-derealization disorder, fMRI, Large-scale brain network

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Introduction

Imagine a world where the sense of self and reality becomes a fleeting, ephemeral experience. This is the world inhabited by individuals with Depersonalization-Derealization Disorder (DPRD). Unlike more commonly studied psychiatric disorders, DPRD often evades clear clinical understanding and diagnosis, drifting into the grey area of psychiatric nosology [1]. This disorder is defined by a sustained sense of estrangement from one's identity (depersonalization), situating it as a primary disturbance of the self [2, 3] or from the surrounding environment (derealization), positioning it as a primary

disruption of familiarity. Such characteristics fundamentally challenge our understanding of human consciousness. DPRD significantly affects cognitive and emotional functioning [4–6], thereby heavily burdening affected individuals. The elusive pathogenesis of DPRD has hindered the development of effective treatments, underscoring the urgent need for comprehensive investigations into its neural mechanisms.

Previous studies have identified altered functional activity in specific brain regions associated with DPRD, such as the right anterior cingulate (ACC) [7], bilateral medial prefrontal cortex (mPFC) [7], and temporoparietal junction (TPJ) [8–11], the insula [12] and the dorsolateral prefrontal cortex (DLPFC) [13]. These findings provide insights into the neural correlates of DPRD. Studying large-scale brain networks has opened new vistas in understanding the neurobiological basis of various psychiatric disorders. These networks, encompassing distributed but functionally connected brain regions, offer insights into the complex interplay between different areas of the brain. In conditions such as schizophrenia, bipolar disorder, and major depressive disorder, studies on these networks have not only enhanced our understanding of disease mechanisms but also shown potential in diagnostic applications. Recent neuroimaging studies on the dissociative subtype of PTSD show significant dysfunction in large-scale networks, especially the somatomotor network [14]. There's hyperconnectivity in trauma-related dissociation and changes in the default mode and sensorimotor networks during autobiographical memory retrieval [15]. These disruptions in sensory, motor, and self-referential processing may be central to dissociative experiences. However, the application of this research to DPRD remains scant, leaving a significant gap in the understanding and diagnosis of this disorder.

Integrating machine learning into our study is a strategic move to navigate the complexity of psychiatric data. Its capability to uncover hidden patterns in extensive datasets makes it a promising tool for understanding altered functional connectivity in brain networks and evaluating their diagnostic potential.

Given the limited understanding of neural mechanisms in DPRD, we conducted an exploratory analysis to investigate potential alterations in large-scale brain networks and their associations with clinical symptoms. This exploration may provide insights into potential biomarkers for DPRD diagnosis. To conduct the exploration, we planned to recruit drug-naïve DPRD patients and healthy controls (HCs) and detect resting-state functional scans. Then, we calculated within-and between-network functional connectivity (FC) using the Schaefer et al. [14] and Tian et al. [15] atlas. The Support Vector Machine (SVM) model was employed to classify DPRD patients and provide features for DPRD patients concerning dysfunctional large-scale brain networks. Finally, the correlation analysis was performed between altered FC of large-scale brain networks and scores on the Cambridge Depersonalization Scale (CDS) in DPRD patients.

Methods

The Ethics Committee of Beijing Anding Hospital, Capital Medical University, China, approved this study. The protocol was carried out under the guidance of the Declaration of Helsinki.

Participants

This study encompassed 47 drug-naïve, right-handed patients diagnosed with DPRD and 49 HCs meticulously matched for age, gender, and education. Diagnosis of DPRD in patients adhered to the International Classification of Diseases, Tenth Revision (ICD-10) criteria, specifically F48.1, which aligns with our previous study [16]. Participants were thoroughly screened utilizing the Mini-International Neuropsychiatric Interview (M.I.N.I.) [17].

Inclusion criteria for DPRD patients were: (a) aged between 18 and 40 years (to minimize the confounding effects of age-related brain changes while ensuring capacity for informed consent); (b) first episode and drug-naïve; (c) right-handedness; (d) a score of 70 or higher on the CDS [18], which is a well-validated cutoff score with high sensitivity (75.7%) and specificity (87.2%) for diagnosing DPRD as demonstrated by Sierra & Berrio [18]; (e) providing a signed informed consent form. Exclusion criteria encompassed: (a) current or history of anxiety disorder, major depressive disorder, or posttraumatic stress disorder; (b) a history of organic pathologic changes; (c) a history of substance addiction or brain trauma; (d) any MRI contraindications.

HCs were recruited through solicitation, screened using the M.I.N.I., and evaluated with the 2-item version of the CDS [1] to ensure the absence of previous DPRD symptoms or psychiatric diseases. Additionally, all HCs were confirmed to have no acute or chronic disease history.

Clinical assessment

We used the CDS total and factor scores to evaluate DPRD symptoms. The CDS, described by Sierra and Berrios (2000), is a comprehensive self-assessment tool designed to measure the frequency and duration of depersonalization experiences over a preceding six-month period. This measure employs a graduated scoring system, ranging from 0 (indicating 'Never') to 4 ('All the time') for frequency and from 1 (lasting a few seconds) to 6 (spanning 'more than a week') for the duration. Higher

scores on the CDS are indicative of more frequent or prolonged episodes of depersonalization.

Previous factor analytic studies of the CDS have revealed its multidimensional nature, with various proposed factor structures including two- [19], four- [20], and five-factor [21] models. For this study, we adopted the five-factor model established by Simeon et al. [21]— comprising numbing, unreality of self, perceptual alterations, unreality of surroundings, and temporal disintegration—to facilitate a more nuanced exploration of the correlations between altered networks and the clinical manifestations of DPRD.

MRI data acquisition

This study obtained neuroimaging data using a 3.0 Tesla MRI scanner (Prisma 3.0; Siemens, Germany) at Beijing Anding Hospital, Capital Medical University, China. The imaging protocol employed a single-shot, gradient-recalled echo-planar imaging (EPI) sequence, characterized by the following parameters: repetition time (TR) of 2000 ms, echo time (TE) of 30 ms, flip angle set at 90°, a matrix size of 64×64, a field of view (FOV) of 200 mm×200 mm, a slice thickness of 3.5 mm with an inter-slice gap of 1 mm, covering 33 axial sections, and totaling 240 volumes. Additionally, high-resolution brain structural images were acquired using a T1-weighted three-dimensional (3D) multi-echo magnetization-prepared rapid gradient-echo (MPRAGE) sequence. This sequence featured an echo time of 3.39 ms, a TR of 2530 ms, a slice thickness of 1.3 mm, a voxel size of $1.3\times1\times1$ mm^3, an FOV of 256×256 mm^2, and comprised 128 volumes.

Before the scanning procedure, all participants were instructed to abstain from any addictive substances, including caffeine, nicotine, and alcohol, on the day of the scan. A preparatory period of 30 min of rest was mandated before scanning to ensure participant readiness. During the scanning process, participants were advised to remain immobile, keep their eyes closed, and avoid falling asleep. Foam head holders were utilized to minimize head movement, ensuring the neuroimaging data's accuracy and reliability. The participants underwent MRI scanning for approximately 15 min, including resting-state fMRI acquisition, T1-weighted structural imaging scan, additional time for subject preparation, machine warm-up, and transitioning.

Image preprocessing

All image preprocessing was completed by DPABISurf, which was based on fMRIPrep 20.2.5 [22], FreeSurfer 6.0.1 [23, 24], ANTs 2.3.3 [25], FSL 5.0.9 [26], AFNI 20160207 [27], SPM12 [28], PALM alpha115 [29], GNU Parallel [30], MATLAB (The MathWorks Inc., Natick, USA), Docker (https://docker.com), and DPABI [31]. The default preprocessing pipeline with DPABISurf was used, including converting the user-specified data into Brain Imaging Data Structure (BIDS), skull-stripping, spatial normalization, brain tissue segmentation, surface reconstruction for T1-weighted images and slice-timing correction, realignment, head-motion estimation and spatial registration for functional images. The detailed methods were described in the articles by Yan et al. [32] and Oscar et al. [22]. Although DPABISurf was primarily designed for surface-based analysis of cortical structures, it also includes robust functionalities for processing and analyzing subcortical structures, enabling comprehensive whole-brain analyses including both cortical and subcortical regions. Thus, we chose the DPABISurf to conduct image preprocessing.

Network analysis

Initially, we constructed a brain functional network for each subject, aligned with the large-scale functional atlas [33] outlined by Schaefer et al. [34] (400 parcels, cerebral cortex) and Tian et al. [35] (54 parcels, subcortex). Each node of the atlas was a sphere with a radius of 5 mm. A 5 mm radius sphere represented each node in the atlas. The average blood oxygen level-dependent (BOLD) signals across all voxels within the 454 regions of interest (ROIs) were extracted. We then determined the FC between each pair of ROIs by converting Pearson's correlation coefficients of the BOLD signals using Fisher's r-to-z formula. This process resulted in a 454×454 matrix for each subject. The network analyses were carried out using DPABINet [31].

Subsequently, we performed a large-scale FC analysis across eight networks: Visual Network (VN, 62 ROIs), Somatosensory-Motor Network (SMN, 74 ROIs), Dorsal Attention Network (DAN, 46 ROIs), Ventral Attention Network (VAN, 44 ROIs), Limbic Network (LN, 26 ROIs), Frontoparietal Network (FPN, 44 ROIs), Default Mode Network (DMN, 104 ROIs), and Subcortical Network (SCN, 54 ROIs). ROIs were assigned to specific networks based on the well-validated Yeo 7-network parcellation scheme [33], with the additional incorporation of subcortical regions (see Supplementary materials for detailed ROI-to-network mappings).

Statistical analysis

The two-sample t-test was employed to compare FC values between the two groups, controlling for sex, age, education level, and head motion (mean framewise displacement). Cohen's f2 value was used to gauge the effect size. For the group comparison of functional connectivity values, significance was determined using permutation testing (5000 permutations) with a false discovery rate

(FDR) threshold of < 0.05 to correct for multiple comparisons [29]. Similarly, for correlation analyses between functional connectivity measures and clinical variables, all *p*-values were corrected using FDR correction to control for multiple comparisons.

Machine learning diagnose model

We meticulously integrated the observed differences in network FC using the subject-level FC features into a Support Vector Machine (SVM) model. First, we employed leave-one-out cross-validation (LOOCV) for model training and hyperparameter tuning, holding out one sample per iteration as the test set while using the rest for training. This approach optimized the model using the entire dataset. However, it can be computationally demanding for large datasets since it requires n iterations. In this study, the sample size makes the computational cost manageable, making LOOCV the best choice for model evaluation.

After finalizing the model through the LOOCV process, we then performed a single 80/20 train-test split of the full dataset. The 80% training partition was used to train the final model, and the remaining 20% test set was used for an unbiased evaluation of the model's performance. This two-step process ensured that the test set was completely held out from the model development phase.

The model underwent a comprehensive automatic parameter tuning process for its kernel, C, and gamma settings, optimizing its performance. The model's efficacy was evaluated using the Receiver Operating Characteristic (ROC) curve and accuracy metrics. To further enhance the interpretability of the model, we identified the top five most influential FCs by SHAP (Shapley Additive exPlanation) values. These critical FCs were then correlated with clinical symptoms using a Pearson matrix, providing insights into the most impactful FCs concerning the clinical manifestations. The SVM modeling was executed utilizing Python programming.

Results

Demographic and clinical characteristics

In this study, a cohort consisting of 47 patients diagnosed with DPRD (12 females) and 49 HCs (14 females) were enrolled. Statistical analysis revealed no significant differences between the DPRD patients and HCs regarding sex, age, or educational attainment (all *p*-values > 0.05), as detailed in Table 1. Additionally, Table 1 encompasses the CDS of the DPRD patient group.

Large-scale network analysis

This study comprehensively analyses both within-network and between-network FC values between the DPRD and HC groups. Our findings revealed the decreased FCs among DPRD patients across various networks, specifically between the VN and the SMN, VN and DAN, VN and VAN, VN and LN, VN and DMN, SMN and DAN, SMN and LN, SMN and DMN, DAN and LN, DAN and FPN, DAN and DMN, DAN and SCN, VAN and LN, VAN and FPN, VAN and DMN, LN and FPN, LN and DMN, as well as between FPN and DMN. We also observed decreased within-network FCs involving the VN, SMN, LN, and FPN. The effect sizes, represented by Cohen's f2 values, are depicted in the upper triangle of Fig. 1 (Left). A medium effect size was observed in the connectivity between the VN-LN and DAN-LN networks.

SVM model and the influential feature selection

The SVM model was successfully trained with a high degree of accuracy. The model performed exceptionally well on the training data, achieving an accuracy of 0.96. Additionally, the model could generalize well to new data, achieving an accuracy of 0.8 on the test set. An ROC curve was plotted to evaluate the model's performance,

Table 1 Clinical Information of DPRD patients and HCs

	DPRD($n=47$)	HC($n=49$)	t/×2	P(two-tailed)
Sex(M/F)	35/12	35/14	0.011	0.92
Age(years)	24.11(5.55)	23.05(5.01)	−0.98	0.329
Education(Years)	14.06(2.69)	15.24(3.83)	1.75	0.083
CDS				
Total	166.13(45.66)	-		
Numbing	29.64(14.65)	-		
Unreality of self	39.38(13.61)	-		
Perceptual alterations	20.11(12.78)	-		
Termporal disintegration	22.36(10.12)	-		
Unreality of surroundings	15.19(4.77)	-		

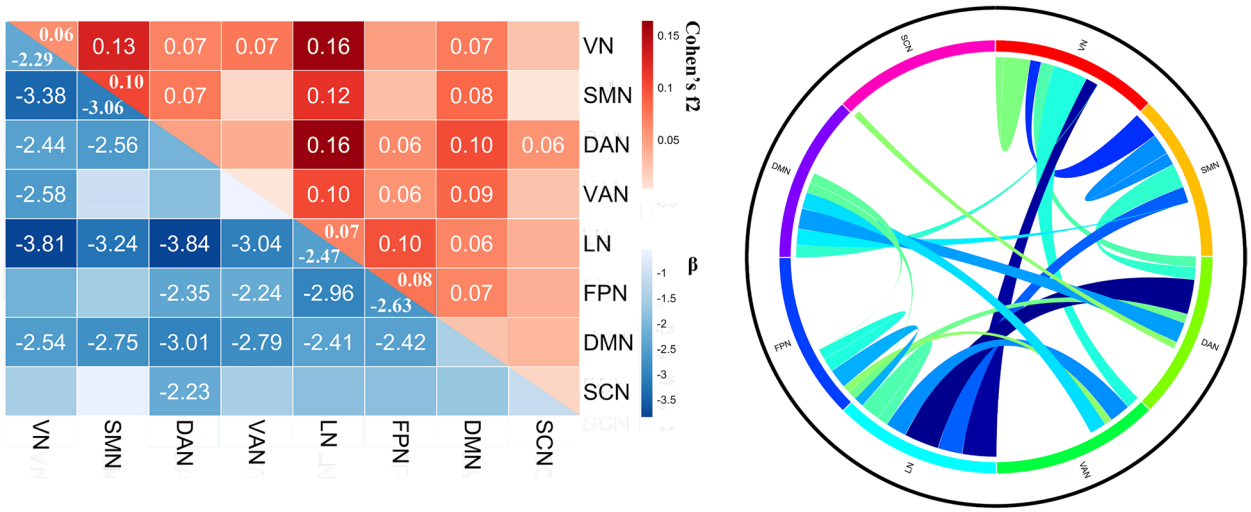

Fig. 1 Large-scale Network Analysis. Abbreviations: VN, visual network; SMN, somatosensory-motor network; DAN, dorsal attention network; VAN, ventral attention network; LN, limbic network; FPN, frontoparietal network; DMN, default mode network; SCN, subcortical network

which visually depicts the trade-off between true positive rate and false positive rate for different classification thresholds. The ROC curve for the model is presented in Fig. 2, which shows that the model performs well across different threshold values.

The SHAP values of the network FCs are depicted in Fig. 3. Notably, the most influential FCs identified were between DAN and DMN, VN and LN, within the SMN, between the VN and DMN, and between DAN and LN.

Correlation analysis

The correlation analysis between the identified five within- and between-network FCs and the five factors of CDS was conducted, followed by adjustment using FDR correction. The analysis revealed that the FC within SMN exclusively exhibited a negative correlation with the 'Self' factor of the CDS (Fig. 4).

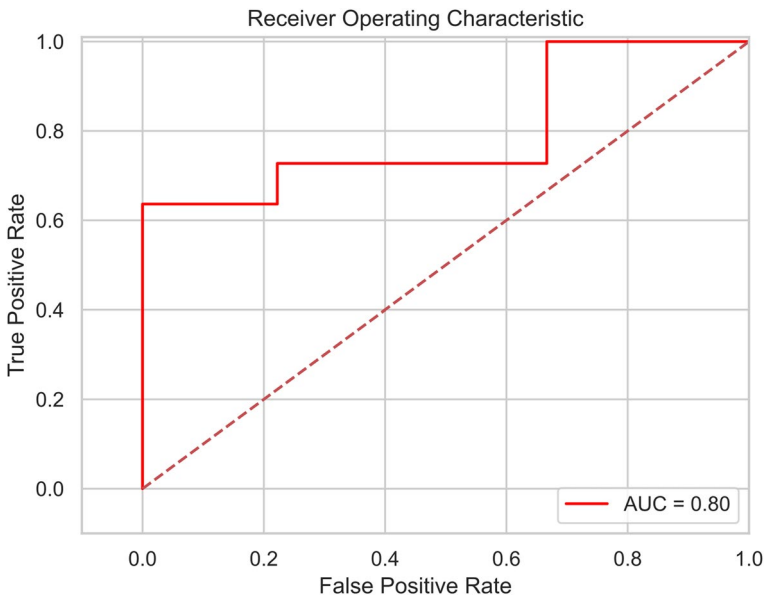

Fig. 2 The ROC curve of SVM

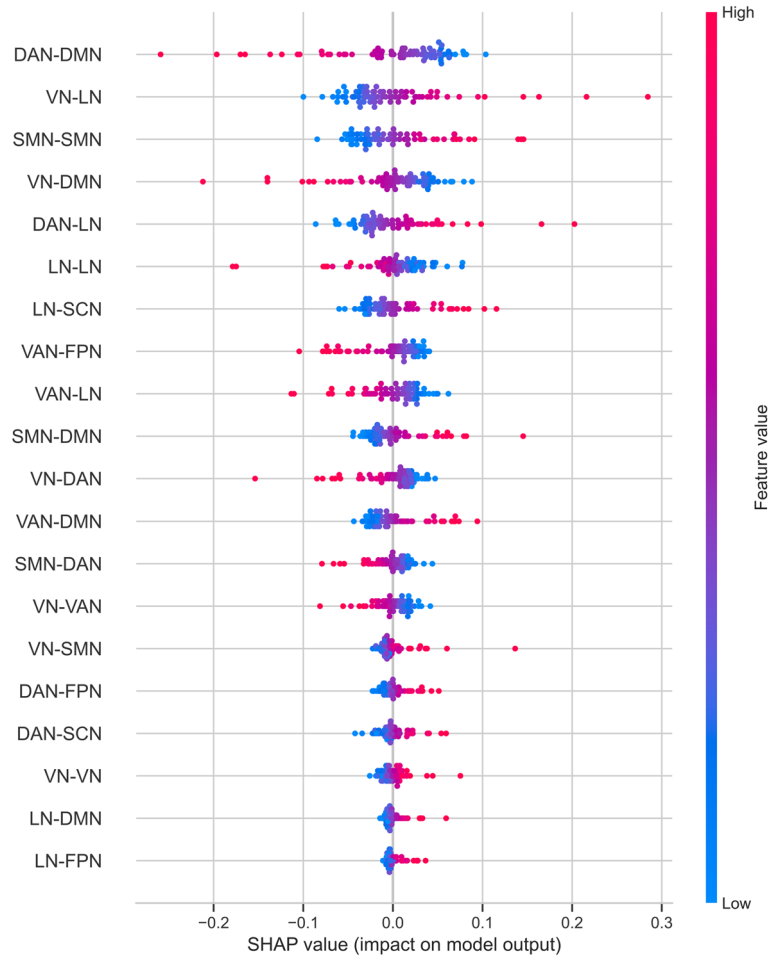

Fig. 3 SHAP value of the SVM. Abbreviations: VN, visual network; SMN, somatosensory-motor network; DAN, dorsal attention network; VAN, ventral attention network; LN, limbic network; FPN, frontoparietal network; DMN, default mode network; SCN, subcortical network

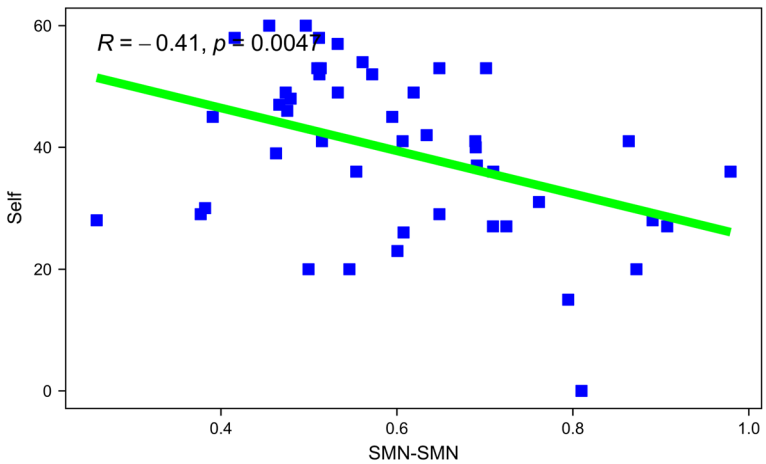

Fig. 4 Correlation analysis between SMN-SMN and Self factor of the CDS. Abbreviations: SMN, somatosensory-motor network

Discussion

This study embarked on a detailed comparison of large-scale networks between patients with DPRD and HCs. Our findings predominantly revealed decreased FC in DPRD patients, specifically noting decreased FCs in 18 between-networks and four within-network. Notably, the between-network FCs of VN-LN and DAN-LN demonstrated a medium effect size. Additionally, we developed an SVM model characterized by high accuracy, through which we identified the most important FCs. Furthermore, our analysis revealed a negative correlation between the 'Self' factor of CDS and SMN connectivity.

The between-network FCs of VN-LN and DAN-LN demonstrated a medium effect size. The notable decreased FC in the VN-LN provides new evidence to support the "visuolimbic disconnection" hypothesis of DPRD [36]. It is characterized by a disruption of communication between visual and limbic structures in the brain (e.g., abnormalities in the amygdala-occipital pathway), which may be a neural correlate of the patient's hyper-emotionality in response to emotionally arousing visual stimuli (difficulty in emotionally coloring visual perceptions). The decreased FC in the visual-limbic system was also negatively correlated with emotional suppression scores by Cao et al. [37]. Corroborating our findings, prior research [7, 12, 38–40] has demonstrated alterations in the frontal gyri of DPRD patients, particularly in the medial prefrontal gyrus within the LN. Concerning the results related to VN, their alignment with reported symptoms involving the visual system, such as flat or picture-like perception, supports hypotheses integrating visual and bodily self-consciousness [41]. It should be noted that the lack of correlation between VN-LN connectivity and the "numbing" factor of CDS casts doubt on this finding, suggesting the need for further exploration.

DAN was proposed to mediate the top-down guided voluntary allocation of attention to locations or features [42]. Guralnik et al. [4, 5] found that patients with DPRD performed significantly worse than the comparison subjects on certain measures of attention within the context of comparable intellectual abilities. Nevertheless, they performed better on incidental learning. The authors speculated that it was due to the excess of unnecessary information. Our results provide neuroimage evidence for the above hypothesis.

The high accuracy of the SVM model indicated the significance of FC value as a diagnostic feature of DPRD. Besides the VN-LN and DAN-LN connections, our results also highlighted the importance of FC between the DMN and DAN, DMN and VN, and within the SMN in the SVM model. The DMN is associated with self-consciousness [43–45] and is a primary network reflecting resting-state BOLD activity. Abnormalities in the connections between the DMN, DAN, and VN serve as critical diagnostic indicators, emphasizing the significant roles of LN and DAN in DPRD.

Moreover, we also observed a significant correlation between the 'Self' factor and FC within SMN. This factor encompasses symptoms indicative of impaired self-consciousness in DPRD patients, including feelings of detachment, mechanical movements, and disconnection from one's thoughts and voice. This discovery supports previous attempts to neurologically distinguish depersonalization from derealization [46]. This study located the sense of disembodiment and the lack of sense of agency (as described in the 'Self' factor 'Feeling of being outside the body' or 'Feeling mechanical and robotic when moving') in the disruption of parietal regions through neurological patients with similar phenomenological experience. Our findings further suggest the potential involvement of SMN dysfunction in impaired bodily self-consciousness of DPRD. This association suggests a potential link between SMN and bodily self-consciousness, supporting previous research on motor functions and bodily self-awareness [47, 48]. Bodily self-consciousness encompasses aspects of self-identification, self-location, and first-person perspective, with neuroimaging evidence suggesting an involvement of the premotor cortex, intraparietal sulcus, sensorimotor cortices, and the temporoparietal junction (TPJ) in these mechanisms [48]. Clinical trials have also shown the efficacy of repetitive transcranial magnetic stimulation on TPJ in treating DPRD [9, 49], highlighting its potential role in DPRD mechanisms.

This study presents a novel approach to deciphering the potential mechanisms of DPRD through large-scale network analysis. However, several limitations need to be noted. Firstly, our study employed self-report scales to assess depersonalization symptoms and their relationship with altered FCs, which may induce biases due to variations in information discrimination. Future research should consider incorporating objective measures or clinical assessments for a more comprehensive understanding of DPRD symptoms. Secondly, our participant recruitment was restricted to individuals aged 18–40 years to minimize age-related confounding effects on brain function. While this strengthens our internal validity, it may limit the generalizability of our findings to older populations with DPRD. Thirdly, our study only detected altered large-scale networks as features to classify DPRD from HCs using the SVM model. It remained unknown whether these features could classify DPRD from other mental disorders. Hence, patients with other mental disorders would be recruited in future studies.

Conclusion

This study significantly advances our understanding of DPRD by revealing marked reductions in FC within specific brain networks. The application of an SVM model highlighted critical neural connectivities correlating with DPRD symptoms, notably between the 'Self' factor of the CDS and the SMN. These insights enhance diagnostic precision and open new avenues for targeted therapeutic interventions, offering a promising direction for future research and clinical practice in DPRD.

Abbreviations

ACC	Anterior Cingulate Cortex
BIDS	Brain Imaging Data Structure
CDS	Cambridge Depersonalization Scale
DAN	Dorsal Attention Network
DPRD	Depersonalization-Derealization Disorder
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
FC	Functional Connectivity
FDR	False Discovery Rate
FPN	Frontoparietal Network
HC	Healthy Control
ICD-10	International Classification of Diseases, Tenth Revision
LN	Limbic Network
LOOCV	Leave-One-Out Cross-Validation
M.I.N.I	Mini-International Neuropsychiatric Interview
mPFC	Medial Prefrontal Cortex
ROC	Receiver Operating Characteristic
ROI	Regions of Interest
SCN	Subcortical Network
SHAP	Shapley Additive Explanation
SMN	Somatosensory-Motor Network
SVM	Support Vector Machine
TPJ	Temporoparietal Junction
VAN	Ventral Attention Network
VN	Visual Network

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06497-w.

Supplementary Material 1.

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Clinical trial number

Not applicable.

Authors' contributions

Author Sisi Zheng analyzed the data and wrote the manuscript. Author Mingkang Song collected the data and wrote the manuscript. Nan Song collected the data. Authors Hong Zhu, Dongqing Yin, Yan Zhao, Meng Fang, and Shanshan Liu provided her expertise in depersonalization-derealization disorder. Authors Yanzhe Ning and Hongxiao Jia contributed to the conception and design, acquisition of data, analysis/interpretation, writing of the article, critical review of the article, and final approval for publication.

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Data availability

The data that support the findings of this study are available from the Beijing Anding Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data is however available from the authors, Sisi Zheng (email address: zhengsisi@ccmu.edu.cn), and Hongxiao Jia (email address: jhxlj@ccmu.edu.cn), upon reasonable request and with permission of the Beijing Anding Hospital.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Beijing Anding Hospital. All participants provided written informed consent. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration.

Competing interests

The authors declare no competing interests.

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