

A Resting-state Functional Magnetic Resonance Imaging Study on Macroscale Topological Properties of Whole-brain Functional Networks in Patients with Post-traumatic Stress Disorder

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Abstract: *Objective:* To investigate alterations in resting-state functional connectivity in patients with post-traumatic stress disorder (PTSD). *Methods:* This was a retrospective case-control study. Forty-five patients with PTSD and 45 healthy control group (HCG) subjects were included. Resting-state functional magnetic resonance imaging (rs-fMRI) scans were performed, and between-group differences in functional connectivity were compared. *Results:* This study did not find significant differences in macroscopic brain network functional connectivity between patients with PTSD and healthy individuals. *Conclusion:* There were no significant between-group differences in global efficiency, mean local efficiency, mean clustering coefficient, or number of rich-club connections of the whole-brain functional network between patients with PTSD and HCG, suggesting that brain network abnormalities in PTSD may not be changes in whole-brain macroscopic topological organization.

Keywords: Post-traumatic stress disorder; Resting-state functional magnetic resonance imaging; Functional connectivity imaging; Graph theory analysis

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1. Introduction

Post-traumatic stress disorder (PTSD) is a delayed-onset psychiatric disorder induced after exposure to severe traumatic events. It is often accompanied by altered brain functional connectivity and represents a chronic mental impairment that persists after trauma exposure^[1]. Resting-state functional magnetic resonance

imaging combined with graph theory analysis can quantitatively describe global information integration, local information segregation, and rich-club core network features of the brain functional network, providing a research approach for elucidating the neural mechanisms of PTSD^[2]. Previous graph theory studies on brain networks in PTSD have yielded controversial results: some studies suggest that PTSD is accompanied by topological reorganization of the whole-brain functional network, whereas other studies have not detected between-group differences, indicating that whole-brain network topological changes in PTSD are not stable^[3–4]. At present, there is still insufficient evidence to clarify whether the whole-brain macroscopic network architecture in patients with PTSD differs from that in healthy individuals.

This study used resting-state functional magnetic resonance imaging to construct a whole-brain functional network. Global efficiency, mean local efficiency, mean clustering coefficient, and number of rich-club connections were selected to compare whole-brain network topological properties between patients with PTSD and a healthy control group (HCG), and to explore whether PTSD involves abnormal functional network organization at the whole-brain level.

2. Materials and methods

2.1. Participants

This was a retrospective case-control study. The PTSD group included 45 patients diagnosed with PTSD in the Department of Psychology of the First Affiliated Hospital of Shihezi University from March 2023 to October 2024. The interval from trauma exposure to enrollment in this imaging examination was 3–24 months for all subjects. The HCG consisted of 45 healthy individuals recruited from the hospital during the same period who were accompanying patients or undergoing routine physical examinations. This study was approved by the Ethics Committee of the First Affiliated Hospital of Shihezi University, approval No. KJ2025-609-01. Subjects signed broad informed consent for magnetic resonance imaging (MRI) examination. All data in this study were de-identified, with no risk of subject privacy disclosure. The study procedures complied with the ethical principles of the Declaration of Helsinki.

Inclusion criteria for the PTSD group: (1) met the diagnostic criteria for PTSD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) of the American Psychiatric Association, with a total score of no less than 22 on the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-5 (PCL-5), confirmed by two psychiatrists; (2) aged 18–60 years, right-handed, with an education level of primary school or above; (3) newly diagnosed PTSD, without having received any trauma-related medication or psychological intervention.

Inclusion criteria for HCG: (1) no history of psychological trauma; (2) aged 18–60 years, right-handed, with an education level of primary school or above.

Exclusion criteria: (1) history of psychoactive substance or drug abuse; (2) mental retardation, intellectual disability, or comorbid other psychiatric disorders (such as schizophrenia, bipolar disorder, etc.); (3) long-term use of medications that may affect cognitive function, including nootropics, benzodiazepines (continuous use for more than 90 days), cholinergic receptor antagonists, etc.; (4) moderate-to-high risk on passive suicide risk assessment; (5) organic parenchymal brain lesions after trauma such as cerebral contusion and laceration, intracranial hemorrhage, and encephalomalacia; (6) pregnant or lactating women.

2.2. Examination and diagnostic methods

2.2.1. General information questionnaire

This study used a self-designed general information questionnaire covering demographic information, handedness, smoking and drinking history, and PTSD diagnosis and treatment history. All surveys were conducted and recorded by trained psychiatrists.

2.2.2. PTSD checklist-5 (PCL-5)

The scale was developed based on the DSM-5 diagnostic criteria for PTSD. It contains 20 items covering four core symptom clusters: symptom cluster B (items 1–5), symptom cluster C (items 6–7), symptom cluster D (items 8–14), and symptom cluster E (items 15–20). The questionnaire uses a 5-point scale: 0 = not at all; 1 = mild; 2 = moderate; 3 = severe; 4 = extreme. Diagnosis of PTSD requires at least: 1 B item (items 1–5), 1 C item (items 6–7), 2 D items (items 8–14), and 2 E items (items 15–20). Each item score ranges from 0 to 4, and the total score ranges from 0 to 80. Higher PCL-5 scores indicate more severe symptoms. For unintentional injury trauma type, the optimal cutoff score is above 22. The scale has good reliability, with an internal consistency Cronbach's α of 0.96 and a test-retest reliability r of 0.84^[5–6].

2.2.3. Scanning methods

Scanning was performed using a GE MR750 3.0 T superconducting MRI scanner with a standard orthogonal head coil. Before scanning, subjects lay in the supine position, wore earplugs to reduce noise interference, and were asked to keep their head as still as possible, remain awake with eyes closed, and breathe naturally and calmly. The scanning environment, noise protection, and head fixation were identical for all subjects, eliminating scanning operation bias. The MRI protocol consisted of routine cranial MRI and functional MRI. First, routine cranial MRI was performed in all subjects, including axial T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), T2-weighted fluid-attenuated inversion recovery (T2-FLAIR), and sagittal T2WI, to exclude organic lesions such as cerebral infarction and space-occupying lesions.

The rs-fMRI (BOLD-fMRI) sequence parameters were: TR = 2000 ms, TE = 30 ms, FOV = 240 mm $\times$ 240 mm, matrix = 64 $\times$ 64, flip angle = 90°, slice thickness = 4 mm, number of slices = 32, slice gap = 0 mm, scan time = 8 min 20 s, including 245 time points.

2.2.4. Data postprocessing

Image postprocessing was performed using the uAI Research Portal (uRP). Raw Digital Imaging and Communications in Medicine (DICOM) data were imported into the platform, converted to Neuroimaging Informatics Technology Initiative (NIfTI) format, and anonymized. Preprocessing included removal of the first 10 time points, slice timing correction, motion correction, co-registration of anatomical images, normalization to standard space, spatial smoothing, temporal filtering (0.01–0.08 Hz), and regression of nuisance signals including motion, white matter, and cerebrospinal fluid. Then, the brain was parcellated into 116 regions based on the Automated Anatomical Labeling (AAL) atlas, and the mean signal time series of each region was calculated. A 116 $\times$ 116 functional connectivity matrix was constructed by calculating Pearson correlation coefficients between each pair of regions. Finally, graph-theoretic metrics were calculated, including global efficiency, mean local efficiency, mean clustering coefficient, and number of rich-club connections.

Blinded manual visual quality control was performed simultaneously. Two researchers with more than

15 years of neuroimaging analysis experience checked the segmentation rendering results case by case on the platform's 3D visualization interface. Samples with contour shift, boundary mismatch, or under/over-segmentation were excluded. The entire analysis was a fully automated pipeline, with no manual tracing or manual parameter adjustment. Image processing personnel were blinded to subject grouping to avoid subjective bias. Thirty samples were selected for a test-retest experiment. According to the Shrout-Fleiss criteria, the intraclass correlation coefficient ICC(3,1) was used to evaluate test-retest reliability of the pipeline. The ICCs for all metrics were 0.961–0.987, and the corresponding 95% confidence intervals overall ranged from 0.922 to 0.992.

2.3. Sample size estimation

G*Power software was used to estimate sample size based on a two-sample independent *t*-test. A two-sided significance level of $\alpha = 0.05$ and power of $1 - \beta = 0.80$ were set. Referring to similar neuroimaging studies, an effect size of Cohen's $d = 0.5$ was selected [7]. Under these conditions, the theoretical minimum sample size was calculated to be 64 per group. Given the strict inclusion and exclusion criteria for PTSD cases in this study, requiring subjects to be newly diagnosed and to have not received any trauma-related medication or psychological intervention, and requiring MRI images to pass strict quality control, recruitment of clinical samples meeting all conditions was difficult. Considering the actual case resources available at the center, 58 PTSD subjects and 56 HCG subjects were initially enrolled. After excluding cases with poor image quality or missing clinical data, 45 subjects were finally included in each of the PTSD and HCG groups. Post hoc power analysis indicated that this sample size had insufficient power to detect a medium effect of $d = 0.5$ and only had good ability to detect medium-to-large effects. Although some observed indicators were subsequently analyzed using two independent samples rank-sum tests, existing literature indicates that sample sizes estimated based on *t*-tests can meet the power requirements of nonparametric tests [8].

2.4. Statistical methods

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 27.0 software (<https://www.ibm.com/spss>). Continuous data were described according to normality test results: normally distributed data are expressed as mean $\pm$ standard deviation, and non-normally distributed data as median (interquartile range); categorical data are described as frequency (percentage). Continuous variables were first tested for normality. When normally distributed, an independent samples *t*-test or Welch's corrected *t*-test was selected according to the variance homogeneity result; when not normally distributed, Mann-Whitney U test (two groups) or Kruskal-Wallis H test (multiple groups) was used.

3. Results

3.1. General clinical data and scales

There were no statistically significant differences in age, sex, or education level between the PTSD group and HCG ($P > 0.05$) (Table 1). The differences in smoking and drinking history between the two groups were statistically significant ($P < 0.01$).

Table 1. Comparison of demographic and clinical characteristics between the PTSD group and the HCG

Variable	PTSD group (<i>n</i> =45)	HCG (<i>n</i> =45)	<i>z</i> / χ^2	<i>P</i> value
Age	44 (22.0)	36 (23.0)	-1.203	0.229
Sex (male/female)	12/33	18/27	1.800	0.180
Education level	1/12/10/22	1/6/8/30	-1.760	0.078
Smoking history (yes/no)	13/32	31/14	14.407	<0.001
Drinking history (yes/no)	16/29	32/13	11.429	0.001
PCL-5 score	59 (17.0)	13 (10.5)	-8.127	<0.001

Note: Education level was grouped as primary school/junior high school/senior high school or technical secondary school/junior college and above; age and PCL-5 scores were analyzed using the Mann-Whitney U rank-sum test; education level was analyzed using the Kruskal-Wallis H test; sex, smoking history, and drinking history were analyzed using the χ^2 test; PTSD, post-traumatic stress disorder; HCG, healthy control group; PCL-5, PTSD Checklist for DSM-5.

3.2. Resting-state brain network functional connectivity analysis

Between-group comparisons were performed for six global graph-theoretic metrics of the whole brain and local network topological parameters of 116 brain regions. The results showed that after FDR correction for multiple comparisons, there were no statistically significant differences in whole-brain global metrics (**Table 2**) or local graph-theoretic metrics of all 116 brain regions between the PTSD group and HCG (all *PFDR* > 0.05).

Table 2. Comparison of graph-theoretic metrics of brain networks between the PTSD group and HCG

Indicator	HCG (<i>n</i> =45)	PTSD group (<i>n</i> =45)	<i>t</i>	<i>P</i>	<i>P</i> value (FDR-corrected)
Global efficiency	0.035 ± 0.010	0.033 ± 0.009	0.848	0.399	0.479
Mean local efficiency	0.018 ± 0.005	0.017 ± 0.004	1.036	0.303	0.479
Mean clustering coefficient	0.013 ± 0.004	0.012 ± 0.003	1.049	0.297	0.479
Number of rich-club connections	3.810 ± 1.541	3.540 ± 1.436	0.859	0.392	0.479
Bridging connections	16.048 ± 5.109	14.977 ± 4.219	1.085	0.281	0.479
Local connections	24.564 ± 6.582	23.676 ± 5.591	0.689	0.492	0.492

Note: Data are expressed as mean ± standard deviation; between-group comparisons used an independent-samples *t*-test; the six metrics were corrected for multiple comparisons using the Benjamini-Hochberg False Discovery Rate (FDR) method. Global efficiency, mean local efficiency, and mean clustering coefficient are dimensionless metrics; the number of rich-club connections, bridging connections, and local connections are expressed as counts (connection edge counts). PTSD, post-traumatic stress disorder; HCG, healthy control group.

4. Discussion

4.1. Analysis of demographic data

Clinical observations have found that patients with PTSD often have higher rates of smoking and drinking, which is consistent with the results of this study^[9]. The high prevalence of smoking and drinking behaviors among patients with PTSD may reflect the self-medication effect of nicotine on PTSD symptoms^[10–11].

4.2. Discussion of negative resting-state functional connectivity results

This study constructed a brain functional network based on resting-state functional magnetic resonance imaging and selected graph-theoretic topological metrics including global efficiency, mean local efficiency,

mean clustering coefficient, and number of rich-club connections to compare brain network organization patterns between patients with PTSD and HCG. The results showed no significant statistical differences in the above network topological parameters between the two groups. Some previous functional brain network studies suggested that PTSD involves an imbalance between brain network integration and segregation, manifested as decreased global efficiency, altered local clustering, or impairment of the rich-club core network, which is considered to be involved in the neural mechanisms of abnormal fear regulation in PTSD. However, this study did not reproduce the above between-group differences, suggesting that topological changes in brain functional networks in PTSD are not stably detectable under all research conditions. The potential reasons for the negative results may include the following:

4.2.1. Clinical heterogeneity of PTSD

PTSD is highly heterogeneous in trauma type, disease course, symptom burden, comorbidity, and medication status. Previous studies reporting abnormal brain network topology mostly included severe, chronic PTSD populations with relatively homogeneous trauma types ^[2, 4]. The sample in this study had a wide range of disease durations, scattered symptom severity distribution, and mixed trauma exposure backgrounds, which may dilute between-group differences in brain network topology. Brain network topological parameters may not be a stable dichotomous feature at the PTSD group level, but may be continuously associated with individual symptom severity.

4.2.2. Brain network construction and threshold selection

Functional brain network topological metrics are highly sensitive to network construction strategies, including atlas selection, edge definition, and thresholding strategy. Under different thresholds, the effect sizes of global efficiency, clustering coefficient, and rich-club structure may change markedly. The threshold settings and network sparsity selections in previous positive studies differ from those in this study, which may lead to inconsistent results ^[12]. At the same time, the number of rich-club connections describes the network connection backbone of core brain regions, and its changes may have a relatively small effect size, making it difficult to detect under the sample conditions of this study.

4.2.3. Sample size and statistical power

Between-group effect sizes of brain network topology are usually small. This study simultaneously tested multiple topological metrics and used multiple comparison correction to control type I error, which reduces test sensitivity and raises the possibility of type II error. The between-group difference in brain network topology between PTSD and HCG is itself weak, and the statistical power of the current sample size is insufficient to identify this between-group difference.

4.2.4. Biological meaning of the metrics

Global efficiency, clustering coefficient, and number of rich-club connections are macroscopic topological metrics of the whole-brain network, reflecting the brain's overall capacity for information integration and segregation. Even if PTSD involves altered functional connectivity in local brain regions, such local connectivity disturbance may not necessarily translate into significant changes in whole-brain macroscopic network topological parameters. In other words, functional connectivity abnormalities in PTSD may be confined to local subnetworks, while the overall network architecture at the whole-brain level remains

relatively stable. This explains the absence of differences in macroscopic topological metrics between the two groups in this study.

4.2.5. fMRI scanning confounders

Resting-state functional magnetic resonance imaging signals are susceptible to head motion interference. Although head motion quality control was performed in this study, residual motion artifacts may still affect the functional connectivity matrix and subsequently interfere with the estimation of brain network topological parameters, potentially masking true between-group differences.

Although no between-group differences were detected, this study still has certain reference value. Current graph theory studies on brain networks in PTSD are dominated by published positive results, with obvious publication bias. The negative evidence provided by this study helps to objectively evaluate the stability of whole-brain macroscopic topological metrics in PTSD research. The results suggest that it is difficult to distinguish patients with PTSD from healthy individuals using only whole-brain macroscopic network topological metrics such as global efficiency, mean local efficiency, mean clustering coefficient, and number of rich-club connections. PTSD-related functional network changes may be more reflected at the local subnetwork level rather than in the overall whole-brain network architecture. Future PTSD brain network research may shift toward local subnetwork topological analysis rather than being limited to whole-brain macroscopic graph-theoretic metrics.

4.3. Limitations

This MRI study still has several limitations. First, a cross-sectional study cannot clarify the causal temporal relationship between brain structural abnormalities and PTSD symptoms or cognitive impairment. Second, the sample size was limited. The sample size in this study was 45 per group, which has limited power to detect a medium effect at the level of Cohen's $d = 0.5$. The positive brain region changes detected in this study mostly involved medium-to-large effects, but some moderate brain structure-cognition associations may still have been missed. Third, brain network topological results depend on the brain atlas and thresholding scheme, and different construction strategies may yield different conclusions. This study did not perform local subnetwork topological analysis, so changes in local networks could not be evaluated. In addition, resting-state fMRI is susceptible to confounders such as subject state during scanning and head motion. Fourth, the sample had a wide range of trauma types and disease durations, and subgroup analyses stratified by trauma subtype or disease course were not performed, making it difficult to resolve disease heterogeneity. Future studies need to expand the sample and conduct longitudinal multimodal imaging stratified research.

5. Conclusion

This study did not find significant between-group differences between patients with PTSD and HCG in whole-brain functional network global efficiency, mean local efficiency, mean clustering coefficient, or number of rich-club connections. This suggests that brain functional network changes in PTSD may not be manifested at the whole-brain macroscopic network architecture level, and it is difficult to distinguish patients with PTSD from healthy individuals using only the above macroscopic graph-theoretic metrics. This study supplements negative evidence on brain networks in PTSD. Future studies may further explore local subnetwork topological features.

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Disclosure statement

The authors declare no conflict of interest.

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