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ORIGINAL RESEARCH

Study on the changes of Structural Covariance Network in post-traumatic stress disorder

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Abstract

The topological properties of functional brain networks in post-traumatic stress disorder (PTSD) have been thoroughly examined, whereas the topology of structural covariance networks has been researched much less. Based on graph theoretical approaches, we investigated the topological architecture of structural covariance networks among PTSD, trauma-exposed controls (TEC), and healthy controls (HC) by constructing covariance networks driven by inter-regional correlations of cortical thickness. Structural magnetic resonance imaging (sMRI) scans and clinical scales were performed on 27 PTSD, 33 TEC, and 29 HC subjects. Group-level structural covariance networks were established using pearson correlations of cortical thickness between 68 brain areas, and the graph theory method was utilized to study the global and nodal properties. PTSD and HC subjects did not differ at the global level. When PTSD subjects were compared to TEC subjects, they had significantly higher clustering coefficient ($p = .014$) and local efficiency ($p = .031$). Nodes having different nodal centralities between groups did not pass the false-discovery rate correction at the node level. According to the structural brain network topological characteristics discovered in this study, PTSD manifests differently compared to the TEC group. In the PTSD group, the SCN keeps the small-world characteristics, but the degree of functional separation is enhanced. The TEC group's reduced small worldness and the tendency for brain network randomization could be signs of trauma recovery.

Keywords PTSD · Cortical thickness · Structural covariance network · Graph theory · Small world

Introduction

Post-traumatic stress disorder (PTSD), also known as a delayed psychogenic response, refers to a delayed and long-lasting mental disorder after a patient experiences severe or catastrophic traumatic events (Francesmonneris et al., 2013). An epidemiological survey shows that the lifetime prevalence of PTSD in China is 4% (Huang et al., 2019). Due to its high prevalence, identifying the neural mechanisms underlying PTSD and its related symptoms has never been more important in terms of facilitating effective prevention and treatment efforts. The changes in brain

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morphology in PTSD patients were confirmed by neuroimaging. Patients with PTSD have reduced prefrontal cortical thickness (Geuze et al., 2008) and increased left angular gyrus cortical thickness (Ross et al., 2021) in comparison to healthy controls (HC). Furthermore, a recent study has linked trauma recovery to an increase in the thickness of the right medial prefrontal cortex (Jeong et al., 2021). Although substantial progress has been made in understanding the structural differences between PTSD and trauma-exposed controls (TEC), little is known about morphological network properties. Analysis of structural covariance networks (SCN) may provide us with a more comprehensive understanding of the pathogenesis of PTSD.

Graph theory is used to analyze the topological characteristics of the brain network (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010). Previous research employing several neuroimaging approaches demonstrated PTSD-related brain network abnormalities (Niu, Du, et al., 2018; Proessl et al., 2020; Suo et al., 2019; Zhu et al., 2019). However, there has been little research into structural covariance networks in PTSD patients. The SCNs reflect the correlation of morphological indicators between brain regions (Chen et al., 2020; Tijms et al., 2012; Zhang J. Chen & Evans, 2008), which have been used in many neurological disease researches, including Parkinson's disease (Guo et al., 2018) and autism spectrum disorder (Cai et al., 2021).

To achieve effective global and local processing, the brain network contains small-world properties (He et al., 2007; Sporns & Zwi, 2004). In some research based on SCNs, small-world properties were observed to be diminished in PTSD. In a study of cortical thickness covariance networks in newly diagnosed PTSD patients, Qi and colleagues discovered that PTSD patients exhibited a lower small-world index than the HC group (Qi et al., 2017). Other research, on the other hand, has found that the small-world index of PTSD remains intact (Niu, Lei, et al., 2018). In addition, the network characteristics have been found changed in maltreated youth with chronic PTSD, suggesting that network centrality differences are evident during the early development of childhood PTSD (Sun et al., 2019). Although graph theory has been used to investigate the SCNs of PTSD patients, the topological properties of their morphological networks remain equivocal. More research into SCNs in the context of PTSD is required.

Studies have shown that the final PTSD pathology results from both pre-disposed and acquired neural abnormalities (Admon et al., 2013). Acquired deficits are identified by comparing individuals with PTSD to individuals without PTSD who have experienced similar traumatic events, distinguishing neural abnormalities specific to the disease from those resulting from the normal stress responses to trauma exposure. Therefore, in addition to healthy controls, subjects with PTSD need to be compared to trauma-exposed subjects without PTSD to control for the lasting effects of acute stressors (Harnett et al., 2020; Stark et al., 2015). Cortical thickness covariance brain networks of PTSD, TEC, and HC groups were constructed in our current research. Graph theory was used to compare the network topology characteristics between groups at the global and nodal levels. We hypothesized that network indicators vary differently across the PTSD and TEC groups. Changes in the nodal characteristics of brain areas related to stress and emotional processing were also expected.

Methods

Participants

Recruitment for the research began in November 2014 and January 2015. A total of 102 subjects were recruited from Wenchang, a city in the Chinese province of Hainan that was devastated by a tropical storm. Everyone signed a written informed consent based on the Helsinki Declaration. At the same time, all subjects were given a protocol that had been approved by Hainan General Hospital's ethical committee.

Only people aged 18 to 65 with right-handedness, no self-described history of head injury, no deficiency of awareness, no major clinical and neurological conditions, no comorbid lifetime, no current psychiatric disorders other than anxiety and depression, no liquor or drug abuse/reliance, no use of mental medicine, and no contraindications to magnetic resonance imaging (MRI) were included in the study. None of PTSD or TEC individuals were getting any psychotherapy or medication at the time of the study. The study eventually comprised 27 PTSD, 33 TEC, and 29 HC participants.

MRI Data Acquisition and Processing

All neuroimaging was conducted at the Hainan General Hospital using a Siemens 3T MR scanner (Skyra, Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. Head motion was reduced using foam pads and a Plexiglas head cradle. Structural MR images were collected for the whole brain with a sagittal 3D-magnetization prepared rapid gradient echo sequences. The parameters included TR/TE = 2300/1.97 ms, field of view = 256 mm, flip angle $\theta = 9°$, matrix = 256 × 256, slice thickness = 1 mm, 176 slices and scan duration = 353 s. These scans were converted to NIFTI format for further processing.

An automatic processing stream termed *recon-all* in the FreeSurfer software package 6.0.0 (http://surfer.nmr.mgh.harvard.edu) was used to reconstruct and estimate the

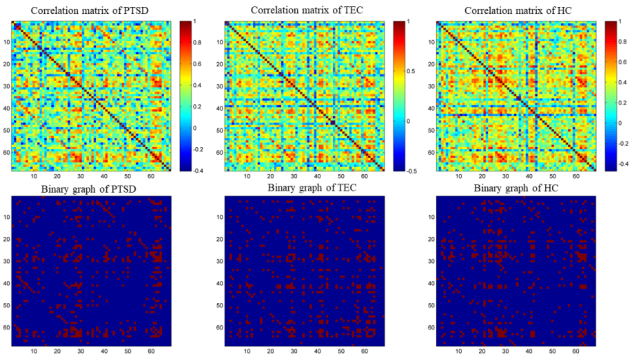

Fig. 1 Correlation matrix of each group of cortex thickness. The upper row is the cortical thickness correlation matrices of PTSD, TEC, HC groups after excluding self-connections. The color bar indicates the strength of the correlation coefficients. The lower row is the binary matrix for each group. PTSD, post-traumatic stress disorder; TEC, trauma-exposed control; HC, healthy control

cerebral cortex of 68 cortical regions (bilateral; 342; Desikan-Killiany Atlas) (Dale et al., 1999; Fischl et al., 1999). Supplementary Material 1 contains specific MRI processing information, and Supplementary Material 2 describes the manual quality control technique.

Clinical measures

The Clinician-Administered PTSD Scale (CAPS) (Weathers et al., 2001) was used to assess symptoms, with the PTSD Checklist-Civilian Version for DSM-IV (PCL-C) being used as a complement (Weathers et al., 1993). Those with PCL scores greater than or equal to 40 were classified as having PTSD, whereas those with PCL scores less than 40 were classified as having TEC. The DSM-IV Structural Clinical Interview was done to see if the patients with PTSD had any concomitant disorders. Additional assessments to characterize the sample included the Self-Rating Anxiety Scale (SAS) for anxiety screening (Zung, 1971), the Self-Rating Depression Scale (SDS) for depression complications screening (Zung, 1965), and the Impact of Event Scale-Revised Scale (IES-R) for assessing subjects' catastrophic experiences of special life events (Weiss, 2007).

Construction of SCNs

The cerebral cortex was divided using the Desikan-Killiany Atlas. In each group, Pearson's correlation coefficients of cortical thickness between any node pairings were calculated to produce a 68-by-68 matrix. Negative weighted edges were set to zero after excluding self-connections (Gong et al., 2012; Sanabria-Diaz et al., 2021). The correlation coefficients greater than the threshold were kept, and the rest were set to 0 according to the predefined threshold sparsity (S = 0.1, 0.01, 0.34) (Zhang et al., 2011). Figure 1 depicts each group's correlation matrix and binary matrix.

Network attributes calculation

Different levels of properties for each threshold were calculated as follows. (1) small-world topology: characteristic path length (L_p), clustering coefficient (C), small-world degree (σ), normalized clustering coefficient (γ), and normalized characteristic path length (λ). The clustering coefficient reveals the network's degree of segregation, while the characteristic path length reflects the network's degree of integration. Small-world networks are characterized by a high clustering coefficient and a short path length (Achard et al., 2006; Watts & Strogatz, 1998). 100 null networks were created to examine the topological features of brain networks. The average clustering coefficient (C_{rand}) and the characteristic path length (L_{rand}) were calculated. Comparing the real network parameters (C_{real}、L_{real}) with the random network parameters, γ ($\gamma = C_{real}/C_{rand}$) and λ ($\lambda = L_{real}/L_{rand}$) were obtained. The σ ($\sigma = \gamma / \lambda$) of the brain network was also calculated. The brain network has a small world if its σ is significantly greater than 1. (2) other whole-brain network attributes: global efficiency (E_{global}) and local efficiency (E_{local}). (3) regional network attributes: nodal efficiency, nodal betweenness, and nodal degree. These three indicators reflect the centrality of the node (Achard & Bullmore, 2007; Freeman, 1977). Formulas and explanations for all these indicators could be found in previous literature (Bullmore & Sporns, 2009). Each network index was calculated repeatedly within the selected density, and a graph was formed with the density as the abscissa and with a certain network parameter as the ordinate. This curve reflected the change of specific network indicators with network density. The area under the curve (AUC) of each network indicator was summarized for further analysis.

Statistical analysis

Demographic and clinical variables

Independent sample *t*-tests, one-way ANOVA, and chi-square (χ^2)tests were performed according to the corresponding types of data ($p<.05$). All the analyses were conducted in IBM Statistics SPSS 26, version 26.0 (IBM Corp, Armonk, NY).

Differences in network metrics

The nonparametric permutation test was used to explore the differences in network topologies between groups (for example, PTSD vs. TEC group). First, the differences

Table 1 The Demographic and Clinical Scores of Three Groups

	PTSD($n=27$)	TEC($n=33$)	HC($n=29$)	p
Demographics				
Gender (males/females)	7/20	7/26	7/22	.909[a]
Age (years)	48.7 ± 10.6	48.6 ± 7.5	49.9 ± 6.2	.791[b]
Education (years)	6.4 ± 3.4	7.00 ± 3.4	9.8 ± 3.3	.001[b]
Clinical data				
SAS score	52.6 ± 10.6	33.1 ± 6.5	28.8 ± 4.4	<.001[b]
SDS score	55.7 ± 10.6	33.0 ± 7.3	27.0 ± 5.8	<.001[b]
PCL-B score	17.2 ± 4.0	10.4 ± 3.2	-	<.001[c]
PCL-C score	19.5 ± 3.0	8.7 ± 1.6	-	<.001[c]
PCL-D score	17.1 ± 3.0	9.9 ± 2.5	-	<.001[c]
PCL total score	53.7 ± 8.5	28.9 ± 5.4	-	<.001[c]
IES-B score	20.7 ± 4.6	-	-	-
IES-C score	16.9 ± 4.5	-	-	-
IES-D score	15.5 ± 3.9	-	-	-
IES total score	52.9 ± 11.2	-	-	-
CAPS-B score	24.5 ± 7.3	-	-	-
CAPS-C score	28.1 ± 8.3	-	-	-
CAPS-D score	25.6 ± 6.8	-	-	-
CAPS total score	78.2 ± 19.3	-	-	-

Data are shown as mean ± SD except for gender, which is presented by the number of each option. PTSD, post-traumatic stress disorder; TEC, trauma-exposed control; HC, healthy control; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; PCL, PTSD Checklist; IES, Impact of Event Scale; CAPS, Clinician-Administered PTSD Scale.

[a] p-value got using a chi-square test.

[b] p-value got with one-way analysis of variance.

[c] p-value got with the independent t-test for continuous variables.

between groups in each network measure were calculated. The correlation matrices of the randomized group were then reconstructed after all individuals were mixed and randomly assigned. Based on these steps, the weight matrices were binarized and the differences in network indicators between groups of the random network were calculated. Permutations were repeated 1000 times at each density to get a distribution of the differences. The p-value was based on the percentile of the real network measures difference ($p < .05$). The Bonferroni correction method was used to control the familywise error rate and the critical value for individual tests was $0.05/\ (3{\cdot}7) = 2.38 \cdot 10^{-3}$. Multiple comparisons between nodes were achieved using false discovery rate (FDR) correction ($p < .05$). In all statistical analysis, the Brain Connectivity Toolbox (https://sites.google.com/ site/bctnet/) (Rubinov & Sporns, 2010) was used in Matlab 2013b to construct and analyze the SCNs. The BrainNet Viewer (http://www.nitrc.org/projects/bnv/) was used to present changes at the regional level.

Results

Cohort characteristics

27 patients with PTSD, 33 TEC, and 29 HC subjects were enrolled in this study (Table 1). There were no statistical differences in terms of gender distribution ($\chi^2 = 0.190$, $df = 2$, $p = .909$) and mean age (F (2,86) = 0.236, $p = .791$). The differences in education level among the three groups was found significant (F (2,86) = 8.255, $p = .001$). The HC group showd higher education level ($p < .005$). Significant differences in terms of SAS (F (2,86) = 80.015, $p < .001$) scores and SDS scores (F (2,86) = 99.425, $p < .001$) were also found. Further analyses showed that PTSD group had higher SAS and SDS scores (all $p < .001$). Among the PTSD patients, 9 subjects had depression comorbidities (seven females and two males), and one subject was diagnosed of anxiety disorder (female). The SDS scores of TEC group were significantly higher than those of HC group ($p < .05$), while no significant difference in SAS scores was found between these two groups ($p = .088$). The total scores of PCL ($t = 13.738$, $df = 58$, $p < .001$), subscale B ($t = 7.052$, $df = 58$, $p < .001$), subscale C ($t = 17.741$, $df = 58$, $p < .001$), and subscale D ($t = 10.131$, $df = 58$, $p < .001$) in PTSD were significantly higher than those in TEC subjects.

Network analyses

Small-world parameters

The results of the whole brain network measurements of the group-specific SCNs are shown in Figs. 2 and 3, and Table 2. The main results are as followed. (1) PTSD vs. HC: Our results indicated no significant difference in γ, λ, and σ values between these two groups ($p > .05$). (2) PTSD vs. TEC: The AUCs of γ, λ, and σ were found no significant differences ($p > .05$). (3) TEC vs. HC: No statistical differences were found on γ and λ ($p > .05$). In addition, the AUC analysis indicated that the σ of the TEC network was smaller than that of the HC group (Fig. 3I, p = .017).

Global Network Measures

The results of the nonparametric replacement test showed no significant difference in the properties of the global network between PTSD and HC subjects. The AUC analysis showed that the clustering coefficient (Fig. 3D, $p = .014$) and local efficiency (Fig. 3E, $p = .031$) of the PTSD group were higher than those of the TEC group. The clustering coefficient (Fig. 3G, $p = .041$) and local efficiency (Fig. 3 H, $p = .027$) of the TEC group were significantly lower than those of the HC group.

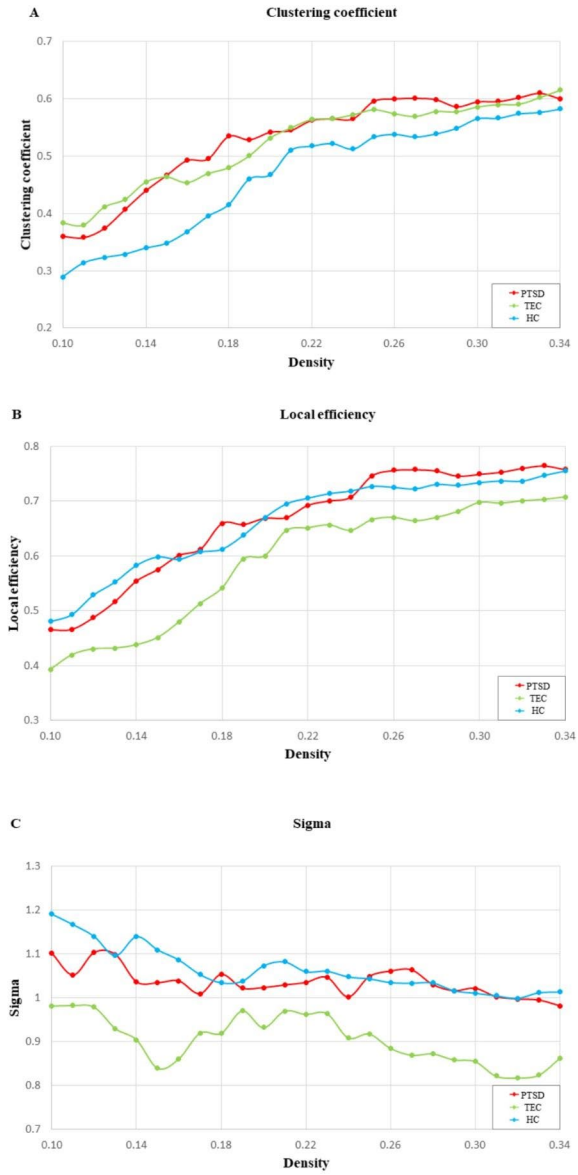

Fig. 2 Significant changes in global network parameters as a function of network density (0.1, 0.01, 0.34). **(A)** the clustering coefficient, **(B)** local efficiency, and **(C)** sigma, small-world index. PTSD, post-traumatic stress disorder; TEC, trauma-exposed control; HC, healthy control

Inter-group comparisons of Regional Network Measures

The AUC analysis of the differences was performed in regional network indicators between the groups. Unfortunately, no nodes survived after the FDR correction. The inter-group comparison of node attributes still revealed the changes in some node characteristics of PTSD patients (Table 3; Fig. 4). The main results are as followed. (1) PTSD vs. HC: Increased nodal centralities in the right isthmus cingulate cortex and the right superior frontal gyrus in patients with PTSD were found. The nodal centrality of the left postcentral gyrus was decreased. (2) PTSD vs. TEC: Compared with the TEC group, the nodal centralities of PTSD on the left rostral middle frontal gyrus, bilateral supramarginal gyrus, and the right temporal pole increased significantly. The nodal degree of the left insula of PTSD was decreased. (3) TEC vs. HC: Compared with the HC group, the nodal centralities of the left postcentral gyrus decreased, while the left insula increased significantly.

Table 2 Global Network Properties between Groups

	PTSD vs. HC	PTSD vs. TEC	TEC vs. HC
C	0.816	0.014	0.041
L_p	0.928	0.285	0.372
E_{global}	0.717	0.243	0.433
E_{local}	0.949	0.031	0.027
γ	0.842	0.227	0.141
λ	0.947	0.550	0.474
σ	0.877	0.304	0.017

C, clustering coefficient; L_p, character path length; $E_{global,}$ global efficiency; E_{local}, local efficiency; γ, normalized clustering coefficient; λ, normalized characteristic path length; σ, small-world index. PTSD, post-traumatic stress disorder; TEC, trauma-exposed control; HC, healthy control.

Discussion

By using the method of graph theory analysis, the regional similarities of cortical thickness were calculated to ascertain the changes in topological characteristics of morphological networks of trauma-exposed patients. As far as we know, this work is the first one to incorporate the SCNs of PTSD, TEC, and HC groups simultaneously. We found that PTSD and TEC groups have different topological characteristics at the global level and nodal level.

4.1 Small World Index Retention in PTSD Patients.

The human brain network is characterized by small-world attributes (Bullmore & Sporns, 2009), which are associated with low construction costs and high-efficiency information dissemination (Achard & Bullmore, 2007). The results of the whole-brain graph theory analysis showed that compared with the HC group, PTSD patients retained the characteristics of small-world topology. It is generally accepted that the small-world organization balances network separation and network integration in information processing (Watts & Strogatz, 1998). Other results have also reported the maintenance of the small-world index in the PTSD group (Zhu et al., 2019). It was noted that the small-world attribute was found to be lower in the TEC group compared with the HC group. Given that the TEC group is resilient to PTSD in this

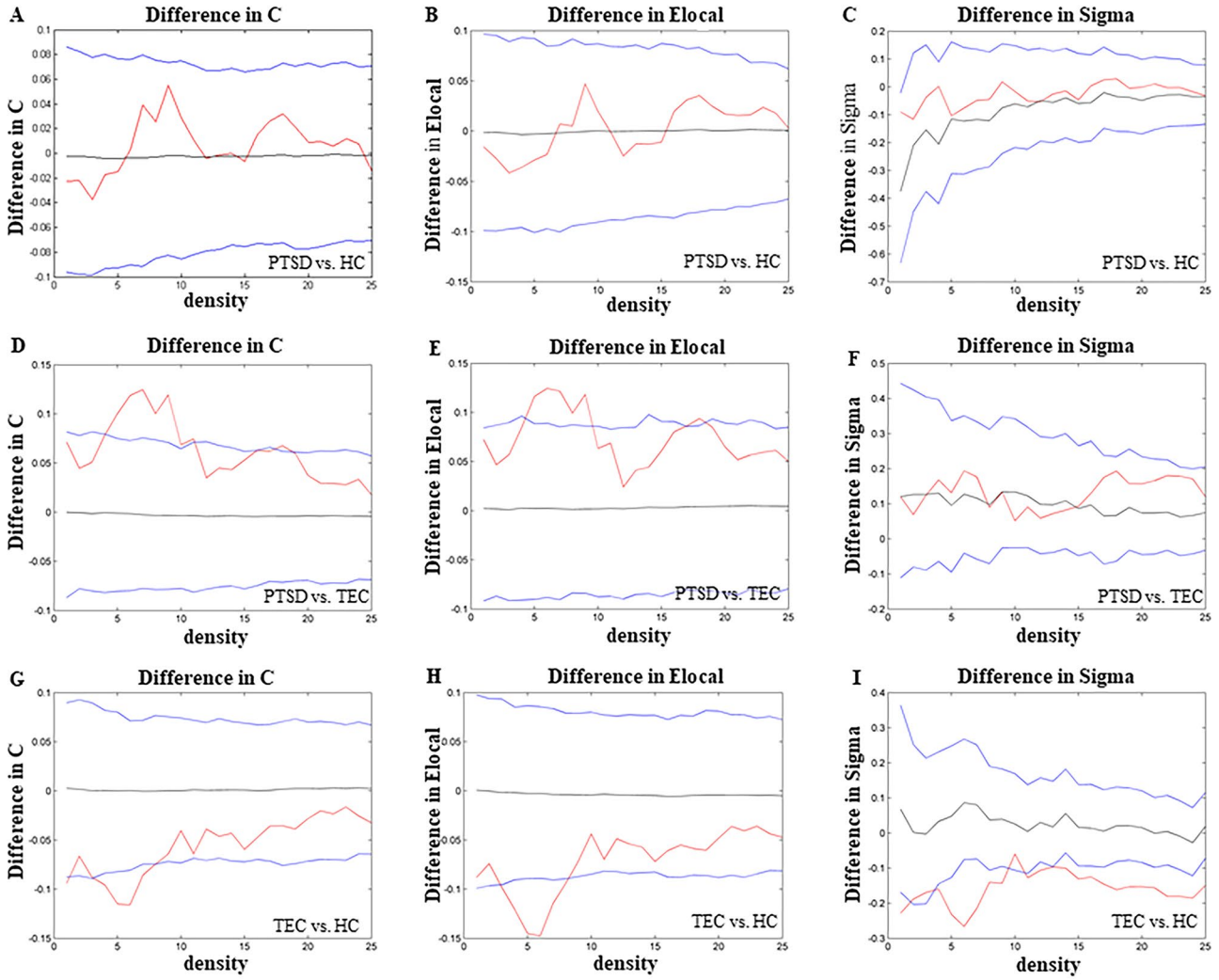

Fig. 3 Differences between groups in global network parameters as a function of network density (0.1–0.34). Clustering coefficient **(A, D, G)**, local efficiency **(B, E, H)**, and small-world index **(C, F, I)** of three SCNs. The 95% confidence interval is represented in upper and lower blue lines, and the black line in the middle is the mean difference after 1000 permutations. The red line represents the true differences between groups, which fall outside the confidence interval indicate significant differences between groups ($p < .05$) under the current threshold. PTSD, post-traumatic stress disorder; TEC, trauma-exposed control; HC, healthy control; C, clustering coefficient; Elocal, local efficiency

case, the reduced small-worldness of the TEC group may be a manifestation of trauma recovery to a certain extent. Additional evidence comes from a study of earthquake survivors. The study found that within 25 days after the earthquake, the survivors' small worldness was found to have decreased compared with the control group, indicating a shift towards a randomized network. In addition, this damage returned to normal after two years (Du et al., 2015).

4.2 Increased functional separation in patients with PTSD.

Our results show that the local efficiency and clustering coefficient of PTSD patients were higher than those of the TEC group, which is consistent with previous studies (Lei et al., 2015; Proessl et al., 2020). The increase in the clustering coefficient denotes higher fault tolerance of the brain when suffering an attack from outside (Brust et al., 2012). Given the inverse relationship between local efficiency and characteristic path length, the increase in local efficiency of PTSD may reflect closer and more effective communication within the network. The increase in local efficiency limits the transmission of information to closely connected specific areas, indicating the increase in network separation in the brains of PTSD patients. The same result was repeated in the functional brain network analysis studies (Zhu et al., 2019). They explored the topological characteristics of the functional connection network of PTSD patients seven years after the earthquake and found that the overall functional separation of the brain network of PTSD patients had increased, which was manifested by a higher normalized clustering coefficient and normalized local efficiency. This

Table 3 The *P*-value for Regions Exhibiting Significant Between-group Differences in Nodal Centralities

	P-value		
Group comparison	Nodal efficiency	Nodal betweenness	Nodal degree
PTSD > HC			
Rh isthmus cingulate	0.042*	0.089	0.092
Rh superior frontal	0.257	0.044*	0.302
PTSD < HC			
Lh postcentral	0.028*	0.012*	0.018*
PTSD > TEC			
Lh rostral middle frontal	0.025*	0.032*	0.037*
Lh supramarginal	0.015*	0.179	0.044*
Rh supramarginal	0.034*	0.195	0.367
Rh temporal pole	0.011*	0.203	0.054
PTSD < TEC			
Lh_insula	0.059	0.268	0.037*
TEC > HC			
Lh insula	0.081	0.032*	0.029*
TEC < HC			
Lh postcentral	0.01*	0.009**	0.023*

Regions were regarded as abnormal if they displayed significant between-group differences in at least one of the three nodal centralities. * $p < .05$, uncorrected. ** $p < .01$, uncorrected. Lh, left hemisphere; Rh, right hemisphere; PTSD, post-traumatic stress disorder; TEC, trauma-exposed control; HC, healthy control

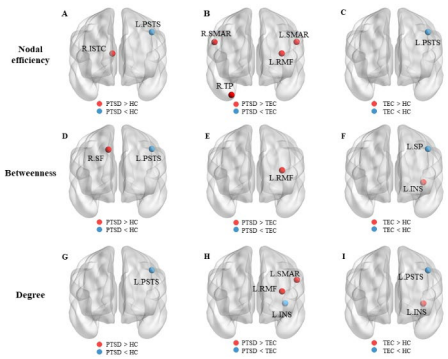

Fig. 4 Regions showing significant between-group differences in nodal centralities ($p < .05$, uncorrected). **(A-C)** nodal efficiency, **(D-F)** betweenness, and **(G-I)** nodal degree. L, left; R, right; ISTC, isthmus cingulate cortex; SF, superior frontal gyrus; PSTS, postcentral gyrus; RMF, rostral middle frontal gyrus; SMAR, supramarginal gyrus; TP, temporal pole; INS, insula; PTSD, post-traumatic stress disorder; TEC, trauma-exposed control; HC, healthy control

research implies that the structural covariance and functional connection networks are consistent to some extent.

The randomization process of neural networks is thought to be a common pattern in some neurological diseases (Lynall et al., 2010). In contrast, the increased local efficiency and clustering coefficient in the current study indicated a more regular brain network in patients with PTSD. Regular patterns of brain networks have also been found in children with PTSD (Suo et al., 2015). However, the SCN of TEC subjects became increasingly random. Specifically, the local efficiency and clustering coefficient of the TEC group was significantly reduced compared with HC. This randomization process may reflect a compensatory adaptation of the brain network when it encounters trauma to cope with the impact of the disease.

4.3 Regional differences between groups.

In addition to the whole brain network indicators, we also explored changes in node centralities at the nodal level. Unfortunately, all nodes did not meet the FDR-corrected threshold. As exploratory research, we excavated some results from the research that cannot be ignored. The TEC group had higher nodal centrality in the left insula than the PTSD and HC groups ($p < .05$, uncorrected for FDR), indicating that the left insula may be a protective factor against PTSD. Previous studies also found that the nodal degree of the bilateral insula in trauma survivors increased significantly (Du et al., 2015). The insula is related to traumatic memory (King et al., 2009). The increased nodal centrality of the left insula may improve the resistance of network topology to some extent, thereby reducing the damage from trauma. A previous study found that a higher regional cerebral metabolic rate of glucose (rcMRglu) in the anterior insula was associated with stronger resilience, which suggests a role for rCMRgu in the anterior insula in resisting the negative effect of trauma (Jeong et al., 2019). These are only our speculations. Follow-up studies need to use clinical data to determine the network characteristics of trauma recovery.

Limitations

There are some limitations to this study. Firstly, some results didn't pass the correction, which might be due to sample constraints and limited capacity for statistical analysis. Expanding the sample size ought to be a premeditated action. Secondly, we only recruited the typhoon-exposed subjects and collected the data five months after the typhoon, and we could not investigate whether these SCNs may also be related to changes in posttraumatic stress between the acute and chronic trauma phases. Time-since-trauma can be a confounding factor in that it's not clear what secondary stressors may occur to augment any TEC vs. PTSD differences.

Conclusions

We compared the structural network topologies among PTSD, TEC, and HC groups based on graph theory. The functional separation of the brain network was intensified in PTSD. Moreover, the decreased small-worldness and the trend of randomization of the SCN in the TEC group may be

a mitigating factor. Our study provides evidence of different network properties in PTSD and TEC subjects, expanding the understanding of trauma-related pathobiology.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s11682-022-00669-y.

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Author contributions Author contributions included conception and study design (YZ and GML), data acquisition (FC and LZ), data processing and statistical analysis (TTX, JK, and RFQ), interpretation of results (TTX, FC, and YZ), drafting the manuscript work or revising it critically for important intellectual content (TTX, FC, YLD, and YZ) and approval of the final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (All authors).

Funding Not applicable.

Availability of data and material Not applicable.

Code Availability Not applicable.

Declarations

Conflict of interest The authors have no conflict of interest to declare.

Ethics approval According to the Declaration of Helsinki, all participants signed written informed consent. At the same time, a protocol, which has been approved by the ethics committee of Hainan General Hospital, was obtained for all subjects.

Consent to participate Informed consent was obtained from all patients for being included in the study.

Consent for publication All authors agree to publish this manuscript which has been read by all of them.

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