Study on the Changes of Structural Covariance Network in Post-traumatic Stress Disorder

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Abstract

It has been widely discussed that the topological characteristics of the functional brain network in post-traumatic stress disorder (PTSD) demonstrates impairments, but the topology of structural covariance network has rarely been studied. Based on graph theoretical approaches, we compared the topological organization of structural covariance networks among PTSD, trauma-exposed control (TEC) group and healthy control (HC) group by constructing covariance networks of cortical thickness. Structural magnetic resonance imaging (sMRI) scans and clinical scales were performed in 27 PTSD, 33 TEC and 29 HC subjects. Based on the cortical thickness correlations, morphological network was constructed and analyzed for each group. Pearson correlation coefficients were computed to explore the relationship of brain network measurements with clinical scales. PTSD and HC subjects did not differ at the global level. Significantly increased clustering coefficient ($p = .014$) and local efficiency ($p = .031$) were observed in PTSD group compared with TEC subjects. At the nodal level, PTSD showed extensive increased nodal centralities in comparison to the other two groups ($p < .05$, uncorrected for false-discovery rate). The structural brain network topological characteristics found in this study suggest that PTSD manifests differently compared to TEC group from pathophysiological perspective. Greater network separation and increased nodal centrality in PTSD patients may be concerning emotional disorders.

Introduction

Post-traumatic stress disorder (PTSD) is a chronic psychiatric disorder (Francesmonneris et al., 2013). An epidemiological survey portrays that the lifetime prevalence of PTSD in China is 4% (Huang et al., 2019). Network-based analysis may provide us with a more comprehensive understanding of the pathogenesis of PTSD.

Graph theory is used for analyzing the topological characteristics of the brain network (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010). According to this method, previous studies using different neuroimaging methods have revealed abnormalities in the brain networks characteristics in PTSD (Niu, Du, et al., 2018; Proessl et al., 2020; Suo et al., 2019; Zhu et al., 2019). As a new method for constructing large-scale brain networks, structural covariance network (SCN), which reflects the correlation of morphological indicators between brain regions (Tijms et al., 2012; Zhang J. Chen & Evans, 2008), has been applied in many neurological diseases research (Cai et al., 2021; Guo et al., 2018).

A healthy brain can balance information integration and specialized processing, that is, it has a small-world topology (He et al., 2007; Sporns & Zwi, 2004). Some studies based on SCN have reported reduced small-world property in PTSD. Qi and colleagues studied cortical thickness covariance networks in newly onset PTSD patients and found that compared with healthy control (HC), PTSD patients had lower small-world index (Qi et al., 2017). However, other studies have revealed that the small-world properties of PTSD remain intact (Niu, Lei, et al., 2018).

Although a few studies have examined the SCN in PTSD using graph theory, study on the topological characteristics of the structural brain network in PTSD remains limited. In addition, trauma-exposed control (TEC) and HC groups, which was essential to distinguish the pathological mechanism between PTSD and general trauma exposure, was not included and studied at the same time.

In our current research, the cortical thickness covariance brain networks of PTSD, TEC and HC groups was constructed. Comparison was thus made on the topological differences between the networks at the global and nodal level by using graph theory. Besides, the association between brain network characteristics and clinical scale in PTSD was explored. We hypothesized that PTSD and TEC groups have different degrees of variations on network indicators. It was also expected that alterations in the nodal properties of brain regions associated with stress and emotional processing. Prediction was made that the changes of SCN are closely related to the severity of clinical symptoms.

Methods

Participants

Recruitment for the research began in November 2014 and January 2015. A total of 102 subjects were recruited from a city named Wenchang in province of Hainan, China, which was severely hit by a tropical typhoon. On the basis of the Declaration of Helsinki, everyone submitted a written informed consent. At the same time, a protocol, which has been authorized by the ethics committee of Hainan General Hospital, were obtained for all subjects.

We only enrolled participants aged 18–65 years old with: right-handedness; no self-detailed history of head injury; no deficiency of awareness; no major clinical and neurological conditions; no comorbid lifetime; no current psychiatric disorder apart from anxiety and depression; no liquor and drug abuse/reliance; no utilization of mental medicine, or contraindications to MRI. At the time of study, none of the PTSD and TEC subjects were receiving any psychotherapy or medication. Eventually, 27 PTSD, 33 TEC and 29 HC subjects were included in the research.

MRI Data Acquisition

All neuroimaging was conducted at the Hainan General Hospital using a Siemens 3T MR scanner 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 $\theta = 9^\circ$, matrix = 256×256 , slice thickness = 1 mm, 176 slices and scan duration = 353 s. These scans were converted to NIFTI format for subsequent analysis.

Clinical Measures

The Clinician-Administered PTSD Scale (CAPS) (Weathers et al., 2001) was tested for evaluating the symptoms, supplemented by the PTSD Checklist-Civilian Version for DSM-IV (PCL-C) (Weathers et al.,

1993). 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) (Weiss, 2007).

Regional Cortical Thickness Measurement

The reconstruction and estimation of the cerebral cortex of 68 cortical regions (bilateral; 34×2; Desikan-Killiany Atlas) were obtained through an automatic processing stream called *recon-all* in FreeSurfer software package 6.0.0 (<http://surfer.nmr.mgh.harvard.edu>) (Dale et al., 1999; Fischl et al., 1999). A 10-mm full-width at half-maximum Gaussian distribution was applied for image smoothing. Subsequently, all images were visually checked layer by layer and manually corrected when necessary.

Construction of SCNs

The Desikan-Killiany Atlas was utilized to divide the cerebral cortex. Pearson's correlation coefficients of cortical thickness between any node pairs were calculated in each group to form a matrix of 68 × 68. After excluding self-connections, negative weighted edges were set to zero (Gong et al., 2012; Sanabria-Diaz et al., 2021). According to the predefined threshold sparsity ($S = 0.1: 0.01: 0.34$) (Zhang et al., 2011), the correlation coefficient greater than the threshold was retained, and the rest were set to 0. Figure 1 showed the correlation matrix and binary matrix of each group.

Network Attributes Calculation

Different levels of properties for each threshold were calculated as followed: (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 cluster coefficient reflects the degree of segregation of the network, and the characteristic path length indicates the extent of network integration. High clustering coefficient and short path length are the characteristics of small-world networks (Achard et al., 2006; Watts & Strogatz, 1998). To evaluate the topological properties of brain networks, 100 null networks were generated and the average clustering coefficient C_{rand} and the characteristic path length L_{rand} were computed. 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, and the σ ($\sigma = \gamma / \lambda$) of the brain network was calculated. If σ is significantly greater than 1, the brain network has a small world. (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

The independent sample t-tests, one-way analysis of variance and chi-square(χ^2) tests were performed according to the corresponding types of data ($p \leq .05$). 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 difference in network topology between groups. Specifically, the difference in the mean value of a certain real measure between groups (for example, PTSD vs. TEC group) was first calculated, then all subjects were mixed and randomly assigned, and the correlation matrix of the randomized group was reconstructed. Based on these steps, the weight matrix was binarized and the difference of indicators between groups of the random network was calculated. 1000 permutations were repeated at each density to get a distribution of the difference. The p value was based on the percentile of the real index difference ($p < .05$). What's more, 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 in regional level.

Relationship between Network Indicators and Clinical Variables

Pearson correlation coefficients were calculated to evaluate the relationship between significant network measurement and clinical scale in patients with PTSD.

Results

Cohort Characteristics

27 patients with PTSD, 33 TEC and 29 HC subjects were enrolled in this study (Table 1). No statistical differences in terms of gender distribution ($\chi^2 = .190$, $df = 2$, $p = .909$) and mean age ($F(2,86) = 0.236$, $p = .791$) was revealed. The test for education level of three groups found significant differences ($F(2,86) = 8.255$, $p = .001$), which was higher in HC group ($p < .005$). 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 revealed. 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, two males), and one patient 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 as to SAS scores was found between these two groups ($p = 0.088$). The total scores of PCL ($t = 13.738$, $df = 58$, $p < 0.001$) and 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 found significantly higher than those in TEC subjects.

Network Analyses

Small-World Parameters

Global Network Measures

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

Inter-Group Comparisons of Regional Network Measures

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

Relationship between Network Indicators and Clinical Variables

In PTSD group, after precluding the interferences of age, gender, education levels and ICV, partial correlation coefficients were computed between the significant brain network indicators and the clinical scales (Fig. 4). The result showed that there existed a significant positive correlation between clustering coefficient and CAPS score ($r = .706, p = .001$). The increased nodal centralities were positively correlated with CAPS score ($r = .676, p = .002$) in PTSD group.

Discussion

By using the method of graph theory analysis, the regional similarity of cortical thickness was calculated to ascertain the changes in topological characteristics of morphological networks of trauma-exposed patients. The relationship between these differences and clinical symptoms was also analyzed. As far as we know, this work is the first one to incorporate the structural covariance network of PTSD, TEC and HC

groups simultaneously. We found that PTSD and TEC groups have different pathophysiological mechanisms, and the topological characteristics of brain network in both groups have changed significantly at different levels.

Human brain network is characterized by small-world attribute (Bullmore & Sporns, 2009), which is associated with high-efficiency information dissemination with low construction cost (Achard & Bullmore, 2007). The results of whole brain graph theory analysis showed that compared with HC group, PTSD patients retained the characteristics of small world topology. It is by now generally accepted that the small-world organization balances network isolation and network integration for information processing (Watts & Strogatz, 1998). Other results have also reported the maintenance of small-world properties in PTSD group (Zhu et al., 2019). It was notable that the small-world attribute was found to be impaired in TEC group. This suggested that trauma could destroy the brain network topology attributes to a certain extent. Although trauma exposure in itself does not meet the diagnostic criteria, it still disrupts the balance of brain isolation and integration. However, it is still unclear whether the changes in small-world properties caused by trauma are temporary or permanent. A study of earthquake survivors found that within 25 days after the earthquake, the survivors' small-world attributes was found decreased compared with control group, indicating a shift towards randomized network, but the damage returned to normal after two years (Du et al., 2015).

Although the overall small-world structure of PTSD patients was similar to that of TEC subjects, their local efficiency and clustering coefficient were higher compared to TEC group, which was in line with previous studies (Lei et al., 2015; Proessl et al., 2020). The increase of clustering coefficient denotes higher fault tolerance of the brain when under attack from outside (Brust et al., 2012). In view of the inverse relationship between local efficiency and characteristic path length, the increase in local efficiency of PTSD may reflect more effective communication within network. The increase in local efficiency limits the transmission of information to closely connected specific areas, indicating the increase of network separation in the brains of PTSD patients. The changes of these global topology indexes were positively correlated with the severity of symptoms, indicating that the increased network separation has clinical significance.

The randomization process of neural networks is thought to be a common pattern in some neurological diseases (Lynall et al., 2010; Stam et al., 2009). In contrast, the increased local efficiency and clustering coefficient in 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). While the networks of TEC subjects became increasingly random.

In addition to the indicators of the whole brain network, we also explored the changes at nodal level. The nodal efficiency of the right isthmus cingulate cortex of PTSD was higher than HC subjects. The alterations in the isthmus cingulate cortex reflect the symptoms of general neurological diseases, namely the impairments in emotional stimulation processing and response capability (Nielsen et al., 2005). Research has shown that PTSD patients have difficulty in emotional response (Wei et al., 2017). It is

interesting to note that the nodal efficiency of the right isthmus cingulate cortex in patients with PTSD was closely related to the severity. Moreover, the nodal centrality in the right superior frontal gyrus of PTSD patients was greater than that of HC group. A similar pattern of results was obtained in previous studies (Sun et al., 2018; Suo et al., 2015). The superior frontal gyrus belongs to the prefrontal cortex and plays a critical role in the emotional brain circuit (Lee et al., 2004). In PTSD group, the higher nodal centrality of the right superior frontal gyrus may represent the neural changes related to emotional response in the brain. It is not clear whether these changes in nodal centrality reflect a pre-onset abnormality of PTSD or a consequence of trauma, since no such change was found in TEC group.

Compared with TEC subjects, PTSD patients demonstrated increased nodal centrality in the left rostral middle frontal gyrus, bilateral supramarginal gyrus and right temporal pole. The rostral middle frontal gyrus is the key brain area of emotion regulation, which is related to fear conditioning (Michalski et al., 2017; Minamoto et al., 2015). The supramarginal gyrus, which belongs to the parietal cortex, is related to emotional processing (Lee et al., 2004). The temporal pole is thought to be an extension of the limbic system (Giordana et al., 2005) that plays a key role in emotional processing (Ezzyat, 2007). In addition, it was also observed that these increased nodal centralities were positively correlated with CAPS scores, suggesting that these nodal lesions may be related to the severity of the disease.

The nodal centrality of the left postcentral gyrus in PTSD group and TEC group was lower than that of HC group, which suggested that this area was related to trauma. The postcentral gyrus is activated during the induction of basic negative emotions (Gilead et al., 2016; Ochsner et al., 2004). Previous studies found that the thickness of the postcentral gyrus decreased in PTSD patients (Lindemer et al., 2013; Liu et al., 2012). The nodal centrality in the left insula in the TEC group was higher than that of PTSD and HC group, suggesting that the left insula may be a protective factor against PTSD. Previous studies also found that the nodal degree of bilateral insula in trauma survivors increased significantly (Du et al., 2015). The insula is related to traumatic memory (King et al., 2009). The increase of nodal centrality of the left insula may improve the resistance of network topology to some extent, thereby reducing the damage of trauma. A previous study found that higher regional cerebral metabolic rate of glucose (rcMRglu) in the anterior insula was associated with stronger resilience, which suggest a role of rCMRgu in the anterior insula in resisting negative effect of trauma (Jeong et al.).

Limitations

There were some limitations in this study. Above all, the results of nodal attributes didn't survive correction, which might be due to sample constraints and limited capacity for statistical analysis. Expanding the sample size ought to be premeditated in future investigations. Secondly, the current research is only for typhoon victims, so it is necessary to be cautious in extending it to other types of trauma. Furthermore, as a cross-sectional study, it was uncertain whether the reported results existed pre-onset or were consequences of the diagnosis. In the future, longitudinal researches are expected to define the causal connection between brain network topology changes and PTSD.

Conclusions

We compared the structural network topology among PTSD, TEC and HC groups based on graph theory. Our results confirmed that different levels of morphological network changes were associated with the severity of PTSD. At the global level, functional segregation of brain networks increased in PTSD patients, and brain networks tend to be regularized. In addition, at the node level, PTSD patients showed extensive changes in nodal centrality, involving the parietal lobe, frontal lobe and temporal lobe which were related to emotional processing. The brain networks of TEC patients tended to be randomized, and the increased nodal centrality of the left insula may be the protective factor of PTSD. Our study expanded the understanding of trauma-related pathobiology and evidenced the overlapping but distinct networks manifestations of PTSD and general trauma.

Declarations

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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, were 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.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors' 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 final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (All authors).

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Tables

Table 1

The Demographic and Clinical Scores of 3 Groups

Characteris	PTSD (n=27)	TEC (n=33)	HC (n=29)	<i>p</i>
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	-	-	-
<p>Data are shown as mean ± SD except 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.</p> <p>^a <i>p</i> value got using a chi-square test.</p> <p>^b <i>p</i> value got with one-way analysis of variance.</p> <p>^c <i>p</i> value got with independent t test for continuous variables.</p>				

Table 2

Global Network Properties between Groups

	PTSD vs. HC	PTSD vs. TEC	TEC vs. HC
C	.816	.014*	.041*
L_p	.928	.285	.372
E_{global}	.717	.243	.433
E_{local}	.949	.031*	.027*
γ	.842	.227	.141
λ	.947	.550	.474
σ	.877	.304	.017*
* represented the $p < .05$. 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.			

Table 3 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	.042*	.089	.092
Rh superior frontal	.257	.044*	.302
PTSD < HC			
Lh postcentral	.028*	.012*	.018*
PTSD > TEC			
Lh rostral middle frontal	.025*	.032*	.037*
Lh supramarginal	.015*	.179	.044*
Rh supramarginal	.034*	.195	.367
Rh temporal pole	.011*	.203	.054
PTSD < TEC			
Lh_insula	.059	.268	.037*
TEC > HC			
Lh insula	.081	.032*	.029*
TEC < HC			
Lh postcentral	.01*	.009**	.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.

Figures

Figure 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.

Figure 2

Significant global network measures of the SCN as a function of network density (0.1:0.01:0.34). Individual graphs show the (A) clustering coefficient, (B) local efficiency, (C) γ , normalized clustering coefficient, (D) λ , normalized characteristic path length, (E) σ , small-world index. PTSD, post-traumatic stress disorder; TEC, trauma-exposed control; HC, healthy control.

Figure 3

Regions showing significant between-group differences in nodal centralities ($p < .05$, uncorrected). Subgraphs show differences for the (A) nodal efficiency, (B) betweenness, (C) degree. Red nodes indicate increased nodal centralities in front group, blue nodes indicate decreased nodal centralities in front groups. 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.

Figure 4

Scatter plots of global and nodal measures against CAPS scores in PTSD with a significant correlation ($p < .05$). L, left; R, right; ISTC, isthmus cingulate cortex; RMF, rostral middle frontal gyrus; SMAR, supramarginal gyrus; TP, temporal pole.