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Original Paper

Typhoon-Related Post-Traumatic Stress Disorder and Trauma Might Lead to Functional Integration Abnormalities in Intra- and Inter-Resting State Networks: a Resting-State Fmri Independent Component Analysis

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Key Words
Post-traumatic stress disorder • Resting-state network • Effective connectivity • Insula • Functional magnetic resonance imaging

Abstract
Background/Aims: Functional connectivity studies based on region of interest approach suggest altered functional connectivity of the default mode network (DMN), executive control network (ECN), and salience network (SN). The aim of this study is to determine whether intranetwork and internetwork brain connectivity are altered in both post-traumatic stress disorder (PTSD) patients and traumatized subjects without PTSD using a data-driven approach. ***Methods:*** Resting-state functional MRI data were acquired for 27 patients with typhoon-related PTSD, 33 trauma-exposed controls (TEC), and 30 healthy controls (HC). Functional connectivity within the DMN, ECN, and SN as well as functional and effective connectivity between these resting-state networks were examined with independent component analysis (ICA), and then compared between groups by conducting analysis of variance. ***Results:*** Within the DMN, the TEC group showed decreased and increased functional connectivity in the superior frontal gyrus compared with the PTSD group and the HC group, respectively. The TEC group showed increased angular functional connectivity within the DMN and decreased functional connectivity in the superior temporal gyrus/posterior insula within the SN relative

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to the HC group. Compared with the TEC group, the PTSD group showed increased functional connectivity in the middle frontal gyrus and supplementary motor area within the ECN as well as in the inferior frontal gyrus/anterior insula within the SN. The PTSD group showed decreased functional connectivity in the supplementary motor area within the SN relative to both control groups. Moreover, the PTSD showed increased excitatory influence from the ECN to DMN compared with both control groups, while the TEC group showed increased inhibitory influence from the DMN to ECN compared with the HC group. Intranetwork functional connectivity within the DMN and SN is altered in traumatized subjects irrespective of PTSD diagnosis. PTSD patients also showed altered intranetwork functional connectivity within the ECN. ***Conclusions:*** Distinct changes of effective connectivity between the DMN and ECN in the PTSD group and TEC group may reflect different compensatory mechanisms for rebalance of resting-state networks in the two groups.

Introduction

In the past several decades, functional neuroimaging studies based on task stimulation have contributed enormously to our understanding of the neurological basis of post-traumatic stress disorder (PTSD)[1, 2]. These researches suggested regional brain function abnormalities in multiple brain areas (e.g., the amygdala, insula, hippocampus, medial prefrontal cortex) in PTSD patients [3-6]. In addition, it is generally accepted that in PTSD patients, increased amygdala activation, decreased medial prefrontal cortex (mPFC) activation and changes in activation of the hippocampus might be associated with an exaggerated response to fear, abnormal emotional regulation and damaged declarative memory, respectively [6-9]. However, increased evidence indicates that local brain function abnormalities cannot comprehensively explain the complicated manifestation of PTSD. By contrast, exploring functional integration between regions may provide an opportunity to better elucidate the neural mechanism of PTSD[10, 11].

Brain regions implicated in PTSD (e.g., the amygdala, hippocampus and dorsolateral prefrontal cortex) are important nodes of the resting-state network (RSN) of the brain [12] that are found by analyzing resting-state functional connectivity [13]. Each network is composed of functionally and structurally connected brain regions [14], which are responsible for their specialized function [15, 16]and remain stable at different time or under different tasks [17, 18]. Among them, the most popular RSNs linked to higher cognitive function are the default mode network (DMN), the salience network (SN) and the executive control network (ECN).

The main brain regions of the DMN are the posterior cingutate/precuneus, mPFC, angular gyrus and hippocampus, which play an important role in self-referencing processing, auto-biographical memory and emotional regulation [19, 20]. The main brain regions of the ECN are the dorsolateral prefrontal cortex (dlPFC) and the lateral parietal lobe, which are involved in memory and executive attention control [16, 21]. SN mainly includes the insular lobe, amygdala and dorsal anterior cingulate cortex (dACC), which is closely associated with conflict detection, reward processing, autonomic and emotional regulation [16, 22]. Furthermore, SN is believed to mediate between ECN and DMN, balancing internally focused process and external information processing [21]. Recently, Menon et al. proposed a triple network model of psychiatric disorders. They believed that a broad range of psychiatric disorders including PTSD can be understood by evaluating dysfunction in the DMN, SN and ECN [23].

Currently, few researchers have analyzed brain function of PTSD patients at the brain network level [24, 25], mostly by utilizing an experimental paradigm based on emotional or cognitive activation tasks. However, task stimulation may lead to increased activation of the amygdala and symptom provocation of PTSD patients [12]. In this respect, functional integration between regions can be better examined with functional connectivity analysis under the resting-state. Sripada et al [12]. used seed-based method to analyze the resting-state functional connectivity of the DMN, SN and ECN. They found that functional connectivity

of the DMN and SN decreased and increased respectively. However, functional connectivity between the DMN and SN brain regions decreased. In light of the region of interest selection bias for the seed based approach, a data-driven analysis known as independent component analysis (ICA), has been developed, which has been previously used to study RSN in vehicle accident-related PTSD [26]. The functional magnetic resonance imaging (fMRI) results indicated that the functional connectivity among RSN in the PTSD group was altered as compared with the control group. However, in this study, individuals that had not been exposed to trauma were selected as controls. Thus, it was very challenging to discriminate changes in functional connectivity of the RSN due to either PTSD or trauma. In our study, we analyzed functional connectivity among the DMN, SN and ECN of typhoon-related PTSD patients using resting-state fMRI and ICA. Furthermore, to indicate whether the functional changes in RSN were either PTSD- or trauma-related, we enrolled trauma-naive and trauma-exposed individuals without PTSD as control groups.

Materials and Methods

Participants and clinical assessment

On July 18, 2014, Typhoon Rammasun, a category 5 super typhoon struck Wenchang city on the island province of China. People residing in this area were heavily affected by this typhoon, which caused at least 14 deaths. Particularly, in Luodou farm of Wenchang city, more than one thousand people were trapped and almost drown by the storm tide induced by this destructive typhoon. We recruited 70 typhoon-exposed subjects from this area, 36 with PTSD (9 males and 27 females) and 34 without PTSD (trauma exposed control, TEC, 7 males and 27 females), who were all screened with the PTSD Checklist-Civilian Version (PCL). PTSD diagnosis was based on DSM-IV diagnostic criteria for current PTSD, and symptoms were assessed with the Clinician-Administered PTSD Scale (CAPS)[27]. The CAPS for DSM-IV is a structured interview assessing the frequency and intensity of each PTSD symptom using behaviorally anchored rating (from 0 to 4). This scale assesses the 17 core PTSD symptoms listed in the DSM-IV and obtains information regarding symptom onset, duration, and functional impact. Absence or presence of comorbid disorders was determined via the Structural Clinical Interview for DSM-IV. Furthermore, 32 healthy controls (HC, 9 males and 23 females) who did not meet DSM-IV Criterion A1 for PTSD were recruited via advertisement from Haikou, a city about 35 km from Wenchang city. For all participants, Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) were administrated to assess anxiety and depression symptoms, respectively. All the above procedures took place between November 2014 and January 2015.

General exclusion criteria included age < 18 years or >65 years, left handedness, a history of head injury or loss of consciousness, significant medical and neurological conditions, comorbid lifetime or current psychiatric disorders other than depression and anxiety, alcohol or drug abuse/dependence, use of psychiatric medication, and contraindications to MRI such as claustrophobia, pregnancy, and ferromagnetic implants. In the PTSD group, completed imaging data were not available for 3 female subjects, and 6 were removed for denture-related artifacts (1 female, 1 male), brain infarction revealed by conventional MRI (1 female), pregnancy (1 female), and excessive movement during MRI scanning (translation >1.5 mm or rotation >1.5° at any direction, 1 male and 1 female). Additionally, we excluded 1 female TEC for excessive movement and 2 male HCs for brain infarction. Thus, 27 PTSD patients, 33 TECs, and 30 HCs were ultimately included in the statistical analysis. The study was in accordance with the declaration of Helsinki, and was approved by the ethics committee of Hainan General Hospital and the Second Xiangya Hospital of Central South University. All participants provided written informed consent after a detailed description of this study.

MRI data acquisition

A 3.0 Tesla whole-body MRI scanner (Magnetom Tim Skyra, Siemens Medical Solutions, Erlangen, Germany) with a 32-channel phased array head coil was used for image acquisition. Subjects' heads were immobilized using a foam pad and a Plexiglas head cradle. High resolution T1-weighted 3D anatomical images were also acquired with a sagittal magnetization-prepared rapid gradient echo sequence for later co-registration and normalization (TR/ TE = 2300/1.97 ms, flip angle =9°, FOV = 256 mm ×256 mm, matrix

= 256 × 256, 176 slices, slice thickness = 1 mm, the total time points=353 sec). BOLD fMRI were prescribed parallel to the anterior commissure-posterior commissure line, which were acquired using a gradient-echo planar imaging (EPI) sequence with an interleaved slice excitation order and a 2 mm isotropic spatial resolution (FOV = 230 mm × 230 mm, matrix = 64 ×64, TR / TE = 2000 ms / 30 ms, flip angle = 90 degree, 35 slices, slice thickness = 3.6 mm, no intersection gap, total volume number = 250, the total time points= 508 sec). During the functional scanning, subjects were instructed to lie quietly, keep eyes closed, and let their mind wander without falling asleep.

Data pre-processing

Preprocessing of the imaging data was carried out using Statistical Parametric Mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm/). The first 10 volumes of the functional images were discarded to ensure signal equilibrium. The remaining 240 volumes were slice-time corrected, realigned, and co-registered with the anatomical scan. The co-registered anatomical images were then segmented into gray matter(GM), white matter (WM), and cerebrospinal fluid (CSF), and normalized into standard Montreal Neurological Institute (MNI) space with a final size of 3 × 3 × 3 mm^3[28]. The resulting normalization matrix was then applied to the functional data. After that, the functional images were smoothed by convolution with an isotropic Gaussian kernel (full width at half maximum [FWHW] = 8 mm). After smoothing, the imaging data were filtered (band pass, 0.01–0.08 Hz) to remove the effects of low-frequency drift and high-frequency noise.

Brain connectivity analysis

Group spatial ICA was conducted by using the infomax algorithm with the GIFT software (http://icatb.sourceforge.net/) in Matlab (The Math Works Inc.). For intranetwork analysis, the *Z* value is a correlation coefficient between the time series of each single voxel and the time series of an independent component. Higher *Z* value indicates stronger functional connectivity. Furthermore, through template matching procedures, the component matched with DMN, ECN and SN (with the highest spatial correlation) best is selected. In the literature, ECN was often divided into the left and right components by ICA, and DMN was often divided into the dorsal, ventral and posterior (abbreviated as dDMN, vDMN and pDMN) [11]. Thus six templates including three DMN templates, two ECN templates and one SN template were used to select the corresponding network component in our study. All of the brain network templates were obtained from the Functional Imaging unit of the Neuropsychiatric Disorders Laboratory at Stanford University, Stanford, California (http://findlab.stanford.edu/functional_ROIs).

To analyze the interactions between RSNs, we extracted time series of dDMN, vDMN, pDMN, left/right ECN and SN. We then used the REST1.8 software to perform functional connectivity analysis and Granger causal analysis. Finally, the 6 × 6 inter-network functional connectivity (Z-value) and effective connectivity measurements were obtained.

Statistics

Chi-squared test was used to analyze gender distribution, and one-way analysis of variance (ANOVA) was performed for all continuous variables except for PCL scores, for which independent t test was used to examine differences between the PTSD group and the TEC group. The above analyses were conducted with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA), with the significance threshold set at $P<0.05$. The following procedures were conducted with SPM8 software to analyze spatial distribution maps of dDMN, vDMN, pDMN, left/right ECN and SN (i.e., intra-network functional connectivity): 1) One sample *t*-test was used to display the distribution characteristics of each target RSN (*P<0.05*, corrected by FWE); 2) Average education years and depression diagnosis were used as covariates in ANOVA, and a post hoc *t* test was confined to the results of one sample *t*-test analysis and ANOVA ($P<0.05$, corrected by AlphaSim). Next, we compared the inter-network functional connectivity and effective connectivity of the 6 RSN among the three groups with the SPSS version 16.0 software, using average education years and depression diagnosis as covariates. The ANOVA result of the inter-network functional connectivity and effective connectivity was multiple corrected by false positive correction with an alpha value of $P<1/30 = 0.033$. Finally, for brain regions with grouPdifference in intra-network functional connectivity, inter-network functional connectivity or effective connectivity, average *Z* value, actual *Z* value and Granger causality value (i.e., the path coefficient) were

extracted, and Pearson's correlation analysis was performed to explore the association between these measurements and the clinically administered PTSD scale (CAPS) score. An alpha value of *P<0.05* (without correction) was considered statistically significant.

Results

Demographic and clinical variables

The demographic and clinical characteristics were summarized in Table 1. There is no significant difference in age (F = 0.317, P= 0.729) and gender distribution (P= 0.912) among the PTSD,TEC, and HC groups. The education level of HC group was higher than that in the PTSD group and the TEC group (F = 8.396, P<0.001). The mean CAPS total score of PTSD group was 78.2 ± 19.3, and the PCL scores were higher in PTSD group as compared with the TEC group (P<0.001). Ten PTSD patients had current psychiatric co-morbidity: 9 with depression (2 males and 7 females) and 1with anxiety disorder (1 female). Significant differences were also found among the three groups in the SAS (F = 81.864, P<0.001) and SDS scores(F = 101.915, P<0.001). Post hoc analyses revealed that the SAS and SDS scores in the TEC group were significantly higher than those in the HC group, but was significantly lower as compared with the PTSD group.

RSN spatial distribution map

There were 31 independent components extracted by ICA, six of which were believed to correspond to the dDMN, vDMN, pDMN, left/right ECN and SN by template matching analysis. The result of one sample *t*-test illustrated spatial distribution of the 6 RSNs (Fig. 1). The major brain regions included in the networks and the correlation coefficients between the networks and corresponding templates were as follows: the dDMN key brain regions were the dorsal and ventromedial prefrontal cortex (vmPFC), dorsal and ventral anterior cingutate, posterior cingutate and the superior frontal gyrus (SFG), r = 0.59. The vDMN mainly included the vmPFC, ventral anterior cingulate cortex (vACC), angular gyrus and SFG, r = 0.48. The pDMN key brain regions were the posterior cingutate, precuneus and angular gyrus, r = 0.58; the left and right ECN major brain regions

Table 1. Demographic and clinical data of traumatized individuals and healthy controls. [a]*P* value obtained with Chi-square test; [b]*P* value obtained with one-way analysis of variance; [c]*P* value obtained with independent *t* test for continuous variables. Values are given as mean ± SD except for gender, which is presented as a number. 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; CAPS, Clinician-Administered PTSD Scale

	PTSD (n = 27)	TEC (n = 33)	HC (n = 30)	*P* value
Gender (males/females)	7/20	7/26	7/23	0.912[a]
Age (year)	48.4 ± 10.3	48.5 ± 7.5	49.9 ± 6.1	0.729[b]
Education (year)	6.4±3.4	7.0 ± 3.4	9.7 ± 3.3	<0.001[b]
SAS score	65.8 ± 13.3	41.3 ± 8.1	36.0 ± 5.5	<0.001[b]
SDS score	69.6 ± 13.2	41.3 ± 9.1	33.5 ± 7.2	<0.001[b]
PCL score	53.7 ± 8.5	28.9 ± 5.4		<0.001[c]
CAPS total score	78.2 ± 19.3			

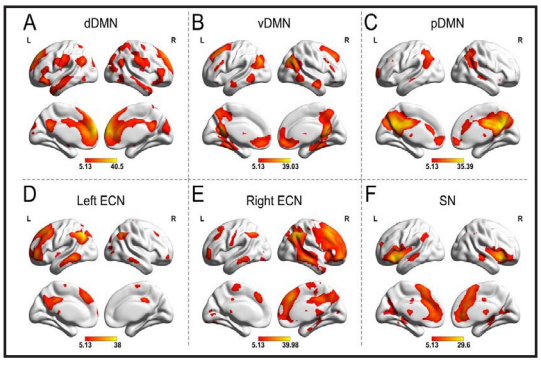

Fig. 1. Results of one-sample t-test in 6 RSNs of all subjects, shown by BrainNet Viewer. A), B), C), D), E) and F) respectively demonstrates the dDMN, vDMN, pDMN, left/right ECN and SN spatial distribution (P<0.05, FEW corrected). dDMN, dorsal DMN; vDMN, ventral DMN; pDMN, posterior DMN; ECN, executive control network; SN, salience network.

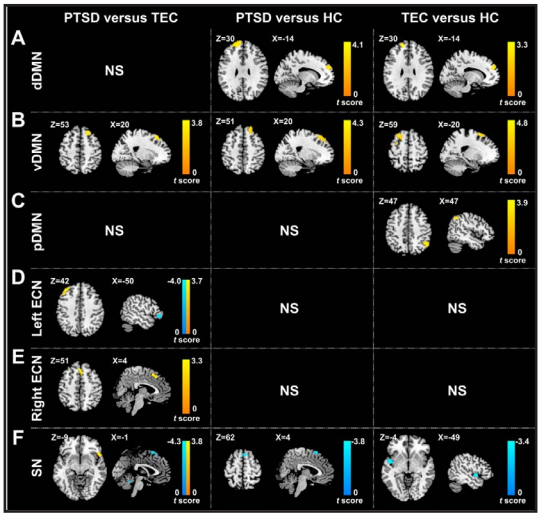

Fig. 2. Comparison of intranetwork functional connectivity among the PTSD, TEC and HC groups. A), B), C), D), E) and F) respectively demonstrates the different internetwork functional connectivity in the dDMN, vDMN, pDMN, left/right ECN and SN (P<0.05, AlphaSim corrected). Warm color represents positive functional connectivity; cold color represents negative functional connectivity. dDMN, dorsal DMN; vDMN, ventral DMN; pDMN, posterior DMN; ECN, executive control network; SN, salience network; PTSD, post-traumatic stress disorder; TEC, trauma-exposed control; HC, healthy control.

were the corresponding SFG, the middle frontal gyrus (MFG) and the dorsal medial prefrontal cortex (dmPFC), with correlation a coefficient of r = 0.62 and r = 0.56, respectively. The SN predominantly included the insular lobe, the inferior frontal gyrus (IFG), dACC, dmPFC and the supplementary motor area (SMA), r = 0.31.

Comparison of intranetwork functional connectivity

Compared with the HC group, functional connectivity of both the left SFG within the dDMN in PTSD group and the TEC group increased (Table 1, Fig. 2A). Within the vDMN, functional connectivity of the right SFG increased as compared with those in the TEC and HC groups. In addition, functional connectivity of the left SFG in the TEC group increased as compared with the HC group (Table 2, Fig. 2B). Within the pDMN, functional connectivity of the right angular gyrus in the TEC group increased as compared with the HC group, (Table 2, Fig. 2C). In the left ECN, functional connectivity of the left MFG in the PTSD group increased as compared with TEC group, whereas that of the right IFG decreased (Table 2, Fig. 2D). In the right ECN, functional connectivity of the bilateral SMA in the PTSD group increased as compared with the TEC group (Table 2, Fig 2E). In the SN, the functional connectivity of the right IFG/anterior insula increased and that of the bilateral SMA decreased in the PTSD group as compared with the TEC group. When compared with the HC group, functional connectivity of the right SMA decreased in the PTSD group, and that of the left superior temporal gyrus (STG)/posterior insula decreased in the TEC group (Table 2, Fig. 2F).

Table 2. Comparison among groups of intranetwork functional connectivity. PTSD, post-traumatic stress disorder; TEC, trauma-exposed control; HC, healthy control; MNI, Montreal Neurological Institute; dDMN, dorsal DMN; vDMN, ventral DMN; pDMN, posterior DMN; ECN, executive control network; SN, salience network; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus

Brain region	PTSD-TEC			PTSD-HC			TEC-HC		
	MNI coordinates (x, y, z)	Vol	*T* value	MNI coordinates (x, y, z)	Vol	*T* value	MNI coordinates (x, y, z)	Vol	*T* value
Left SFG (dDMN)				-15, 51, 30	88	4.12	-15, 54, 30	50	3.31
Right SFG (vDMN)	21, 27, 54	47	3.75	15, 45, 39	84	4.27			
Left SFG (vDMN)							-30, 0, 66	90	4.79
Right inferior parietal lobule/angular gyrus (pDMN)							48, -54, 48	48	3.85
Left MFG(left ECN)	-39, 36, 42	50	3.69						
Left IFG(left ECN)	-51, 36,-6	32	-2.77						
Right SMA(Right ECN)	3, 15, 54	45	3.34						
Right IFG/anterior insula(SN)	54, 18, -12	44	3.76						
bilateral SMA(SN)	6, 18, 66	45	-4.32						
Right SMA(SN)				6, 18, 66	33	-3.78			
Left superior temporal gyrus (STG)/posterior insula(SN)							-48, 0, 0	38	-3.42

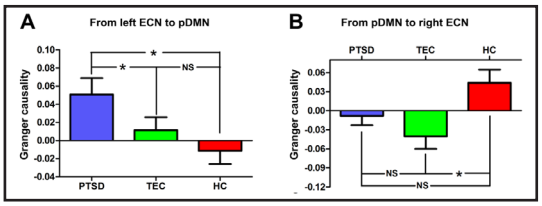

Fig. 3. Comparison of effective connectivity between RSNs. a) As compared with the TEC and the HC group, the excitatory effect of the left ECN on pDMN increased in the PTSD group; B) Compared with the HC group, the inhibitory effect of pDMN on the right ECN increased in the TEC group (P<0.033).

Comparison of the internetwork functional connectivity and effective connectivity

Functional connectivity among the dDMN, vDMN, pDMN, left/right ECN and SN was not significantly different among the three groups. Compared with the TEC and HC group, activation in the left ECN in the PTSD group predicted subsequent increased activity of the pDMN. The influence of the left ECN on pDMN was not significantly different between the two control groups (Fig. 3A). Compared with the HC group, activation in the pDMN in the TEC group also predicted subsequent decreased activity of the right ECN. In the HC group, activation in the pDMN predicted subsequent increased activity of the right ECN (Fig. 3B). SN effective connectivity was not significantly different for the pDMN, dDMN, vDMN and left/right ECN.

Correlation analysis results

The Pearson correlation analysis demonstrated that intra-network functional connectivity (mean *Z* values) of RSNs for regions with group difference, effective connectivity between the pDMN and left/right ECN (path coefficient) were not significantly correlated with the total score of CAPS.

Discussion

In this study, we analyzed the intranetwork functional connectivity of the RSN, the internetwork functional connectivity and the effective connectivity of typhoon-related PTSD, TEC and HC based on the resting-state fMRI and ICA. We found that the functional connectivity within the DMN and SN was altered in PTSD patients and the TEC, as did functional connectivity within the ECN in PTSD patients. The influence of ECN on DMN in PTSD patients also changed, and the influence of DMN on the ECN in the TEC group was abnormal. The results indicated that PTSD and trauma might lead to functional integration abnormalities intra- and inter- RSNs.

Previous resting-state fMRI studies of DMN in PTSD patients demonstrated a decreased inter-network functional connectivity between brain regions [12, 26, 29, 30]. In this study, we found no decrease in functional connectivity within the DMN in PTSD patients. We only found an increase in the functional connectivity of SFG in the DMN as compared with the TEC and HC groups. Generally, important nodes of DMN predominantly include the posterior cingutate/precuneus, mPFC and the angular gyrus. Through DMN-related meta-analysis, Spring et al. found that the lateral prefrontal cortex and the cortical occipital lobe were also core brain regions of this network [20]. Consistent with our study, Reuven et al. reported that resting-state functional connectivity between the left SFG and DMN classical brain region increased as compared with the TEC group [31]. Furthermore, large-scale structural and functional connectivity research indicated that local parameters of the SFG in PTSD patients were higher than those in the HC and TEC groups [32, 33]. Bluhm et al. used resting-state fMRI to investigate childhood trauma-related PTSD. As compared with the TEC group, functional connectivity of the posterior cingutate/precuneus, the mPFC, inferior parietal lobule and the hippocampus decreased. However, functional connectivity increased in the left SFG. The functional connectivity of the posterior cingutate/precuneus was positively correlated with the dissociation experience score of the patients [29]. Therefore, an increase in functional connectivity might be related to observed dissociation symptoms of PTSD patients. However,

in our study, we also found that functional connectivity of the SFG and angular gyrus increased as compared with the HC group. The angular gyrus is related to semantic processing. It is a high level center integrating multisensory, sensorimotor and cognitive function. Blanke et al. reported that stimulating the angular gyrus (i.e., the temporo-parietal junction) in normal healthy people induced an out-of-body experience, suggesting that this brain region was also related to dissociation [34]. Previous fMRI and diffusion tensor imaging (DTI) research reported increased activation of the angular gyrus [3, 35] and damage to the integrity of the local white matter fiber tracts [36] in PTSD patients, respectively. However, in our study, functional connectivity of the angular gyrus was not significantly different between the PTSD and the HC group, which might be related to different research methods and the small sample size. Nonetheless, based on changes in the functional connectivity of the angular gyrus and SFG, we believed that trauma could induce changes in the functional connectivity in DMN, while PTSD could further aggravate injury to brain function. Similarly, recent resting-state fMRI studies reported that the functional connectivity within the DMN in the PTSD and TEC groups significantly decreased as compared with the HC group [37].

The results also showed that functional connectivity of the MFG and SMA within the ECN in the PTSD group increased as compared with the TEC group. As key brain regions of the ECN, MFG and SMA are related to cognitive function (e.g., memory) and emotional regulation, which often show increased activation during execution and cognition related tasks [38, 39]. Currently, research of ECN in PTSD patients is mainly based on task design. Few studies have explored resting-state activity of this network. With a large sample size, a resting-state fMRI study based on low frequency amplitude index indicated that the right MFG in the patients with earthquake-related PTSD had significantly increased activity as compared with the TEC group [40]. Contradictory to observations from resting-state studies, results of this task-based study indicated decreased MFG activation or functional connectivity in the PTSD patients. Rabinak et al. used fMRI and emotional control tasks to investigate war-related PTSD. They found that MFG activation in PTSD patients decreased as compared with the TEC group, suggesting that its inhibition of negative emotion was damaged [41]. Based on fMRI and a working memory task, Daniels et al., revealed that functional connectivity within the DMN in the PTSD group increased as compared with the control group, whereas functional connectivity within the ECN decreased, suggesting that switching between the DMN and ECN caused by a specific task was abnormal [25]. Since the TEC group was not enrolled, researchers could not confirm whether alteration in functional connectivity of the DMN and ECN was caused by trauma or PTSD. However, combined with our study and prior studies of local brain function, we believed that changes in brain function of the ECN is altered specifically in PTSD. Consistent with this assumption, structural MRI indicated that gray matter volume of the MFG and SMA decreased in PTSD patients [42, 43], suggesting that changes in MFG structure was related to PTSD rather than trauma [44]. Above all, based on the results of ECN in our study as well as decreased functional connectivity of DMN in PTSD in the literature, increased functional connectivity within ECN in our study suggested an imbalance between DMN and ECN under resting-state condition. Interestingly, when PTSD patients had received therapy, symptom improvement was accompanied by lateral orbitofrontal and SMA changes, which suggested therapy-associated reversion of ECN [45].

The comparison of functional connectivity within the SN indicated that in the PTSD group, functional connectivity of the right IFG/anterior insula increased as compared with the TEC group, and that of SMA decreased as compared with the TEC and HC groups. Posterior IFG and the anterior insula are core brain regions of the SN, and play a very important role in predicting negative stimulus and emotional processing [46]. In this study, an increase in the functional connectivity of the IFG/anterior insula may reflect persistent hypervigilance of the patient. Consistent with our study, research based on fMRI of emotional stimulation task reported increased activation of the anterior insula in the PTSD [47]. Functional connectivity research also indicated that functional connectivity of the anterior insula and other SN brain regions increased in PTSD patients [12, 48]. SMA is involved in motion control and down-regulation of negative emotion [45]. Therefore, decreased functional connectivity of

SMA within the SN in PTSD patients may be related to inhibition of this brain region on SN brain regions (e.g., the amygdala), serving as a compensatory mechanism of emotional regulation in PTSD patients. Consistent with this conclusion, we previously found that effective connectivity between the SMA and amygdala was abnormal. Furthermore, Cisler et al. found that functional connectivity of the amygdala and SMA were negatively correlated with the PTSD symptom score [49]. It should be noted that functional connectivity of the STG/posterior insula in the TEC group decreased as compared with that of the HC group. The difference in results of the anterior and posterior insular lobe was associated with their differential functions. The anterior insular lobe is mainly involved in advanced awareness and cognition processing, while the posterior insular lobe is involved in sympathetic nerve control and visceral sensation processing [22]. Decreased functional connectivity of the STG/posterior insular lobe may reflect enhanced attention on external threatening stimuli and decreased inner somatic sensation and auditory sense processing in trauma survivors [50]. Moreover, Tursich et al. explored the association between PTSD symptom severity and functional connectivity within and between networks. They found that the hypervigilance score was negatively associated with functional connectivity of the STG/posterior insular lobe within the SN[11].

In addition to functional connectivity within the DMN, ECN and SN, we also explored interactions between RSNs. We found that in the PTSD group, excitatory effect of the left ECN on pDMN increased as compared with the TEC and HC groups, and the inhibitory effect of the pDMN on ECN in the TEC group increased as compared with the HC group. Given decreased functional connectivity of DMN in PTSD patients and TEC group [12, 26, 29, 37] and increased functional connectivity of ECN in PTSD patients found in our study, we believed that effective connectivity changes in the DMN and ECN might represent a compensatory regulation of the brain function when the balance in the resting-state was disrupted. However, different compensatory mechanisms might exist in PTSD patients and the TEC group, with the former group through promoting the excitatory influence of ECN on DMN, and the latter group through inhibitory effect of DMN on ECN. Partly consistent with our results, Tursich et al. found that functional connectivity between the DMN and ECN were associated with PTSD symptom severity [11]. Furthermore, Kennis et al. studied veterans using resting-state fMRI and found that the functional connectivity between the vACC (important node of DMN) and MFG (key node of ECN) increased in the TEC group as compared the HC group [51]. This observation suggested that changes in the interaction between DMN and ECN were active responsiveness to traumatic stress, which was protective factor for not developing PTSD. However, effective connectivity between DMN and ECN in PTSD patients or TEC was not examined by other studies at this time. Thus our results and explanations still require verification.

Above all, our study indicated that irrespective of PTSD diagnosis, there is abnormal functional connectivity within and between RSNs in trauma sufferers. Trauma can lead to increased functional connectivity within DMN, and PTSD can aggravate such functional damage. The changes in functional connectivity within the DMN might be associated with dissociation symptoms of the trauma sufferers. Changes in functional connectivity within the ECN in PTSD patients suggested an imbalance between DMN and ECN. Changes in the functional connectivity within the SN in trauma sufferer might be associated with hypervigilance, increased attention to external stimulus, and decreased processing of primary sensory information. In addition, changes in effective connectivity between DMN and ECN in PTSD patients and TECs might indicate a differential brain function compensatory mechanism.

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Disclosure Statement

Thea authors declare to have no competing interests.

References

1 Wolf RC, Herringa RJ: Prefrontal-Amygdala Dysregulation to Threat in Pediatric Posttraumatic Stress Disorder. Neuropsychopharmacology 2016;41:822-831.
2 Boccia M, D'Amico S, Bianchini F, Marano A, Giannini AM, Piccardi L: Different neural modifications underpin PTSD after different traumatic events: an fMRI meta-analytic study. Brain Imaging Behav 2016;10:226-237.
3 Sartory G, Cwik J, Knuppertz H, Schurholt B, Lebens M, Seitz RJ, Schulze R: In search of the trauma memory: a meta-analysis of functional neuroimaging studies of symptom provocation in posttraumatic stress disorder (PTSD). PLoS One 2013;8:e58150.
4 Stark EA, Parsons CE, Van Hartevelt TJ, Charquero-Ballester M, McManners H, Ehlers A, Stein A, Kringelbach ML: Post-traumatic stress influences the brain even in the absence of symptoms: A systematic, quantitative meta-analysis of neuroimaging studies. Neurosci Biobehav Rev 2015;56:207-221.
5 Zoladz PR, Diamond DM: Current status on behavioral and biological markers of PTSD: a search for clarity in a conflicting literature. Neurosci Biobehav Rev 2013;37:860-895.
6 Shin LM, Rauch SL, Pitman RK: Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann N Y Acad Sci 2006;1071:67-79.
7 Hughes KC, Shin LM: Functional neuroimaging studies of post-traumatic stress disorder. Expert Rev Neurother 2011;11:275-285.
8 Rauch SL, Shin LM, Phelps EA: Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research--past, present, and future. Biol Psychiatry 2006;60:376-382.
9 Hayes JP, Hayes SM, Mikedis AM: Quantitative meta-analysis of neural activity in posttraumatic stress disorder. Biol Mood Anxiety Disord 2012;2:9.
10 Rabinak CA, Angstadt M, Welsh RC, Kenndy AE, Lyubkin M, Martis B, Phan KL: Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. Front Psychiatry 2011;2:62.
11 Tursich M, Ros T, Frewen PA, Kluetsch RC, Calhoun VD, Lanius RA: Distinct intrinsic network connectivity patterns of post-traumatic stress disorder symptom clusters. Acta Psychiatr Scand 2015;132:29-38.
12 Sripada RK, King AP, Welsh RC, Garfinkel SN, Wang X, Sripada CS, Liberzon I: Neural dysregulation in posttraumatic stress disorder: evidence for disrupted equilibrium between salience and default mode brain networks. Psychosom Med 2012;74:904-911.
13 van den Heuvel MP, Hulshoff Pol HE: Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 2010;20:519-534.
14 van den Heuvel MP, Mandl RC, Kahn RS, Hulshoff Pol HE: Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. Hum Brain Mapp 2009;30:3127-3141.
15 Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME: The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 2005;102:9673-9678.
16 Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD: Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27:2349-2356.
17 Laird AR, Fox PM, Eickhoff SB, Turner JA, Ray KL, McKay DR, Glahn DC, Beckmann CF, Smith SM, Fox PT: Behavioral interpretations of intrinsic connectivity networks. J Cogn Neurosci 2011;23:4022-4037.
18 Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, Beckmann CF: Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 2009;106:13040-13045.

19 Andrews-Hanna JR: The brain's default network and its adaptive role in internal mentation. Neuroscientist 2012;18:251-270.
20 Spreng RN, Mar RA, Kim AS: The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. J Cogn Neurosci 2009;21:489-510.
21 Sridharan D, Levitin DJ, Menon V: A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci U S A 2008;105:12569-12574.
22 Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A: Functional connectivity of the insula in the resting brain. Neuroimage 2011;55:8-23.
23 Menon V: Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 2011;15:483-506.
24 Lanius RA, Frewen PA, Tursich M, Jetly R, McKinnon MC: Restoring large-scale brain networks in PTSD and related disorders: a proposal for neuroscientifically-informed treatment interventions. Eur J Psychotraumatol 2015;6:27313.
25 Daniels JK, McFarlane AC, Bluhm RL, Moores KA, Clark CR, Shaw ME, Williamson PC, Densmore M, Lanius RA: Switching between executive and default mode networks in posttraumatic stress disorder: alterations in functional connectivity. J Psychiatry Neurosci 2010;35:258-266.
26 Zhang Y, Liu F, Chen H, Li M, Duan X, Xie B: Intranetwork and internetwork functional connectivity alterations in post-traumatic stress disorder. J Affect Disord 2015;187:114-121.
27 Weathers FW, Keane TM, Davidson JR: Clinician-administered PTSD scale: a review of the first ten years of research. Depress Anxiety 2001;13:132-156.
28 Spati J, Hanggi J, Doerig N, Ernst J, Sambataro F, Brakowski J, Jancke L, grosse Holtforth M, Seifritz E, Spinelli S: Prefrontal thinning affects functional connectivity and regional homogeneity of the anterior cingulate cortex in depression. Neuropsychopharmacology 2015;40:1640-1648.
29 Bluhm RL, Williamson PC, Osuch EA, Frewen PA, Stevens TK, Boksman K, Neufeld RW, Theberge J, Lanius RA: Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. J Psychiatry Neurosci 2009;34:187-194.
30 Chen AC, Etkin A: Hippocampal network connectivity and activation differentiates post-traumatic stress disorder from generalized anxiety disorder. Neuropsychopharmacology 2013;38:1889-1898.
31 Reuveni I, Bonne O, Giesser R, Shragai T, Lazarovits G, Isserles M, Schreiber S, Bick AS, Levin N: Anatomical and functional connectivity in the default mode network of post-traumatic stress disorder patients after civilian and military-related trauma. Hum Brain Mapp 2016;37:589-599.
32 Long Z, Duan X, Xie B, Du H, Li R, Xu Q, Wei L, Zhang SX, Wu Y, Gao Q, Chen H: Altered brain structural connectivity in post-traumatic stress disorder: a diffusion tensor imaging tractography study. J Affect Disord 2013;150:798-806.
33 Suo X, Lei D, Li K, Chen F, Li F, Li L, Huang X, Lui S, Kemp GJ, Gong Q: Disrupted brain network topology in pediatric posttraumatic stress disorder: A resting-state fMRI study. Hum Brain Mapp 2015;36:3677-3686.
34 Blanke O, Arzy S: The out-of-body experience: disturbed self-processing at the temporo-parietal junction. Neuroscientist 2005;11:16-24.
35 Flatten G, Perlitz V, Pestinger M, Arin T, Kohl B, Kastrau F, Schnitker R, Vohn R, Weber J, Ohnhaus M, Petzold ER, Erli HJ: Neural processing of traumatic events in subjects suffering PTSD - a case study of two surgical patients with severe accident trauma. Psychosoc Med 2004;1:Doc06.
36 Schuff N, Zhang Y, Zhan W, Lenoci M, Ching C, Boreta L, Mueller SG, Wang Z, Marmar CR, Weiner MW, Neylan TC: Patterns of altered cortical perfusion and diminished subcortical integrity in posttraumatic stress disorder: an MRI study. Neuroimage 2011;54 Suppl 1:S62-68.
37 DiGangi JA, Tadayyon A, Fitzgerald DA, Rabinak CA, Kennedy A, Klumpp H, Rauch SA, Phan KL: Reduced default mode network connectivity following combat trauma. Neurosci Lett 2016;615:37-43.
38 Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U: Neural network of cognitive emotion regulation--an ALE meta-analysis and MACM analysis. Neuroimage 2014;87:345-355.
39 Ray RD, Zald DH: Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. Neurosci Biobehav Rev 2012;36:479-501.
40 Yin Y, Li L, Jin C, Hu X, Duan L, Eyler LT, Gong Q, Song M, Jiang T, Liao M, Zhang Y, Li W: Abnormal baseline brain activity in posttraumatic stress disorder: a resting-state functional magnetic resonance imaging study. Neurosci Lett 2011;498:185-189.

41 Rabinak CA, MacNamara A, Kennedy AE, Angstadt M, Stein MB, Liberzon I, Phan KL: Focal and aberrant prefrontal engagement during emotion regulation in veterans with posttraumatic stress disorder. Depress Anxiety 2014;31:851-861.
42 Thomaes K, Dorrepaal E, Draijer N, de Ruiter MB, van Balkom AJ, Smit JH, Veltman DJ: Reduced anterior cingulate and orbitofrontal volumes in child abuse-related complex PTSD. J Clin Psychiatry 2010;71:1636-1644.
43 Nardo D, Hogberg G, Lanius RA, Jacobsson H, Jonsson C, Hallstrom T, Pagani M: Gray matter volume alterations related to trait dissociation in PTSD and traumatized controls. Acta Psychiatr Scand 2013;128:222-233.
44 Li L, Wu M, Liao Y, Ouyang L, Du M, Lei D, Chen L, Yao L, Huang X, Gong Q: Grey matter reduction associated with posttraumatic stress disorder and traumatic stress. Neurosci Biobehav Rev 2014;43:163-172.
45 MacNamara A, Rabinak CA, Kennedy AE, Fitzgerald DA, Liberzon I, Stein MB, Phan KL: Emotion Regulatory Brain Function and SSRI Treatment in PTSD: Neural Correlates and Predictors of Change. Neuropsychopharmacology 2016;41:611-618.
46 Sripada RK, King AP, Garfinkel SN, Wang X, Sripada CS, Welsh RC, Liberzon I: Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. J Psychiatry Neurosci 2012;37:241-249.
47 Nardo D, Hogberg G, Flumeri F, Jacobsson H, Larsson SA, Hallstrom T, Pagani M: Self-rating scales assessing subjective well-being and distress correlate with rCBF in PTSD-sensitive regions. Psychol Med 2011;41:2549-2561.
48 White SF, Costanzo ME, Blair JR, Roy MJ: PTSD symptom severity is associated with increased recruitment of top-down attentional control in a trauma-exposed sample. Neuroimage Clin 2015;7:19-27.
49 Cisler JM, Scott Steele J, Smitherman S, Lenow JK, Kilts CD: Neural processing correlates of assaultive violence exposure and PTSD symptoms during implicit threat processing: a network-level analysis among adolescent girls. Psychiatry Res 2013;214:238-246.
50 Koch SB, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M: Aberrant Resting-State Brain Activity in Posttraumatic Stress Disorder: A Meta-Analysis and Systematic Review. Depress Anxiety 2016;33:592-605.
51 Kennis M, Rademaker AR, van Rooij SJ, Kahn RS, Geuze E: Resting state functional connectivity of the anterior cingulate cortex in veterans with and without post-traumatic stress disorder. Hum Brain Mapp 2015;36:99-109.