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# Intranetwork and internetwork functional connectivity alterations in post-traumatic stress disorder

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ABSTRACT

*Background:* A large number of previous neuroimaging studies have explored the functional alterations of post-traumatic stress disorder (PTSD). However, abnormalities in the functional architecture of resting-state networks in PTSD were rarely elucidated.

*Methods:* This study used independent component analysis to explore the resting-state intranetwork and internetwork functional connectivity differences between 20 PTSD patients and 20 matched healthy controls (HCs).

*Results:* Selective alterations of intranetwork and internetwork intrinsic functional connectivities were found in the PTSD patients. Compared with HCs, the PTSD patients exhibited significantly decreased network connectivity within the anterior default mode network, posterior default mode network (pDMN), salience network (SN), sensory-motor network, and auditory network. Furthermore, the PTSD patients exhibited increased internetwork connectivity between SN and pDMN.

*Limitations:* This study lacked recruitment of trauma-exposed HCs, which limits our ability to determine whether the alterations are caused by PTSD or trauma exposure.

*Conclusion:* The findings suggested that the PTSD patients exhibited abnormal functional connectivity at the brain network level. Notably, the enhanced internetwork connectivity between SN and pDMN in the PTSD patients may be associated with hyperarousal and heightened anxiety in PTSD.



## 1. Introduction

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that can develop in individuals who have experienced or witnessed traumatic events (Francati et al., 2007; Hughes and Shin, 2011). Motor vehicle accidents (MVAs) are common traumatic events, and the prevalence rates of PTSD following MVAs have been reported to be approximately 25–33% (Bryant et al., 2000; Harvey and Bryant, 1998; Ursano et al., 1999). MVA survivors may experience a series of potentially trauma-related events, including distressing effects, pain, suffering, and body disfigurement (Delahanty et al., 2000). PTSD is characterized by persistent re-experiencing of the traumatic event, avoidance of reminders of the traumatic event, numbing of general responsiveness, and hypervigilance (DSM-IV-TR) (Blake et al., 1995). Although the symptoms of PTSD are readily identifiable, the exact pathophysiology underlying PTSD remains not fully elucidated.

Previous task-based functional magnetic resonance imaging (fMRI) studies on PTSD patients have shown abnormal activations in the emotion- and cognition-related regions of the brain, including amygdala, insula, medial prefrontal cortex (MPFC), lateral prefrontal cortex, and anterior cingulate cortex (ACC) (Patel et al., 2012; Ramage et al., 2013). Task-based studies have also found differences between PTSD patients and HCs during visual perceptive tasks and auditory tasks (Weber, 2008). Brain regions within sensory networks have already exhibited abnormal activations in PTSD patients. For example, previous studies using picture viewing tasks found that PTSD patients showed abnormal

*Abbreviations:* PTSD, post-traumatic stress disorder; HCs, healthy controls; fMRI, functional magnetic resonance imaging; ICA, independent component analysis; aDMN, anterior default mode network; RSNs, resting-state networks; pDMN, posterior default mode network; lCEN, left central executive network; rCEN, right central executive network; SMN, sensory-motor network; AN, auditory network; SN, salience network; VN, visual network; MPFC, medial prefrontal cortex; STG, superior temporal gyrus

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activations in visual cortex, suggesting the visual sensory processing deficits in PTSD patients (Hendler et al., 2003; Mueller-Pfeiffer et al., 2013). Abnormal activations in auditory cortex and motor cortex have also been found in PTSD patients (Morgan and Grillon, 1999; Whalley et al., 2013).These studies indicated that the brain functional abnormalities in PTSD were associated with widely distributed alterations in the brain. However, other research suggested that the activation patterns of specific brain regions would be insufficient to reveal the complex neurobiology underlying PTSD (Menon, 2011; Tursich et al., 2015). Many previous studies have consistently supported the notion that human behavior and cognition are characterized as emergent properties of coordinated activities in large-scale brain networks (Bressler and McIntosh, 2007; Dosenbach et al., 2007). For example, default mode network (DMN) is thought to be an integrated system for self-related cognition, including self-monitoring, autobiographical memory and social cognitive functions (Spreng et al., 2009). Additionally, Menon (2011) proposed that multiple psychiatric and neurological disorders can be understood by investigating the dysfunction in three networks, namely DMN, salience network (SN), and central executive network (CEN). Thus, the large-scale brain network studies, focused on revealing how disturbances in brain regions operating within large-scale networks contribute to abnormal cognitive and affective functions, would provide novel insights into understanding the pathophysiological mechanisms of psychiatric and neurological disorders (Menon, 2011).

Resting-state functional connectivity (RSFC), which evaluates intrinsic connections between brain regions without confounding effects of cognitive abilities to perform behavioral tasks, has been largely used to elucidate the pathophysiological basis of psychiatric and neurological disorders (Di Martino et al., 2011; Guo et al., 2013; Liu et al., 2014; Woodward et al., 2011). Increasing evidence for abnormal functional connectivity (FC) in intrinsic connectivity networks, such as SN and DMN, has recently been demonstrated in PTSD patients (Liu et al., 2015; Peterson et al., 2014; Sripada et al., 2012). However, traditional RSFC investigated the correlations between the seed regions of interest (ROIs) and other brain regions, which showed temporal synchronization of spontaneous fluctuations in the BOLD signals between any two spatially distinct brain regions (Biswal et al., 1995, 1997; Liu et al., 2013). It may restrain the obtained results because the traditional RSFC is mainly based on the selection of specific seed regions. Hence, whole-brain FC analyses at the network level are needed to reveal the comprehensive functional map of the functional reorganization in PTSD patients. For instance, Jin et al. (2014) divided the whole brain into 90 regions to investigate the abnormal FCs throughout the whole brain in PTSD patients. However, research has shown that the heteromodal regions in the brain, which simultaneously support multiple functions, contain various subregions with distinct connectivity profiles (Etkin et al., 2011; Lee et al., 2005). Many previous approaches based on preselected seeds or large divisions (e.g., 90 regions) may ignore much of the functional complexity.

In the present study, independent component analysis (ICA), a data-driven method constructing large-scale intrinsic networks at the voxel level, was used to investigate the abnormalities of FCs in PTSD. A recent study performed ICA to explore the FCs within and between the DMN, CEN, and SN underlying PTSD symptom dimensions; the findings suggested that the severity of PTSD symptoms was related not only to the reduced connectivity within SN or DMN but also to the reduced connectivity between dorsal anterior DMN (aDMN) and posterior DMN (pDMN), as well as between CEN and DMN (Tursich et al., 2015). Investigations on the intranetwork and internetwork connectivities have provided new insights into the large-scale functional organization in human brains (Buckner and Vincent, 2007; Fox and Raichle, 2007). Abnormal intranetwork and internetwork connectivities have existed in various disorders, including congenital blindness (Wang et al., 2014), multiple sclerosis (Rocca et al., 2014; Schoonheim et al., 2015), and schizophrenia (Calhoun et al., 2009; Yu et al., 2012). However, little is known about the altered intranetwork and internetwork connectivities in resting-state networks (RSNs) among PTSD patients relative to healthy controls (HCs). In the present study, ICA was first applied to obtain RSNs, and six RSNs highly associated with PTSD were finally selected based on previous task-based studies. Group comparisons were then performed to investigate the intranetwork and internetwork differences between PTSD patients and HCs. We hypothesized that the PTSD patients may exhibit abnormal intranetwork and internetwork FCs in RSNs.

## 2. Methods

### 2.1. Participants

This study was approved by the Medical Research Ethics Committee of Southwest Hospital. Written informed consent was obtained from each participant before the experiment. Twenty PTSD patients who suffered from MVAs and twenty healthy individuals were recruited from Southwest Hospital, Third Military Medical University. Each of the PTSD patients had experienced one MVA and witnessed an actual or threatened death with serious injury to others. Twelve of these PTSD patients had body injury and bruises. Participants from the two groups were matched in terms of age, gender, and education. Clinical and demographic data of the participants are listed in Table 1. PTSD diagnosis was evaluated using the Clinician-Administered PTSD Scale for DSM-IV (CAPS-DX) (Blake et al., 1995). Three main kinds of symptoms, namely, re-experiencing, avoidance, and increased arousal symptoms, were evaluated for both frequency and intensity. The severity score of each symptom was calculated by adding the frequency and intensity scores, which were summed by all 17 symptom questions and/or the three symptoms. All the participants were right-handed with $IQ > 80$, as evaluated by the Wechsler Adult Intelligence Scale. None of the participants was diagnosed with any other neuropsychiatric disorder, such as schizophrenia, mental retardation, and epilepsy. No history of head injury was reported among the PTSD patients. Additionally, all PTSD patients had not taken psychotropic medication in the past two months

### 2.2. MRI data acquisition

All fMRI data were obtained by a 3.0 T Siemens MRI scanner (Trio; Siemens Medical, Erlangen, Germany). Foam pads were used to immobilize the head motion of all the participants. Resting-state fMRI data were acquired using the echo-planar imaging (EPI)

**Table 1**
Demographics and clinical characteristics of PTSD patients and HCs.

| Variable (mean ± SD) | PTSD ($n$=20) | HC ($n$=20) | $p$ Value |
|---|---|---|---|
| Gender (M/F) | 13/7 | 14/6 | 0.74[a] |
| Age | 32.92 ± 8.48 | 31.53 ± 7.43 | 0.45[b] |
| Education | 11.20 ± 3.80 | 13.00 ± 2.20 | 0.37[b] |
| IQ | 98.20 ± 5.50 | 103.20 ± 6.30 | 0.24[b] |
| CAPS total score | 52.33 ± 9.44 | 8.26 ± 9.31 | < 0.01[b] |

SD, standard deviation; PTSD, post-traumatic stress disorder; HCs, healthy controls; IQ, intelligence quotient; CAPS, clinician-administered PTSD scale (range 0–136).

[a] The $p$ value was obtained by Chi square test.

[b] The $p$ value was obtained by two-sample $t$ test.