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Research report

Altered brain structural connectivity in post-traumatic stress disorder: A diffusion tensor imaging tractography study

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ABSTRACT

Background: Post-traumatic stress disorder (PTSD) is characterized by dysfunction of several discrete brain regions such as medial prefrontal gyrus with hypoactivation and amygdala with hyperactivation. However, alterations of large-scale whole brain topological organization of structural networks remain unclear.
Methods: Seventeen patients with PTSD in motor vehicle accident survivors and 15 normal controls were enrolled in our study. Large-scale structural connectivity network (SCN) was constructed using diffusion tensor tractography, followed by thresholding the mean factional anisotropy matrix of 90 brain regions. Graph theory analysis was then employed to investigate their aberrant topological properties.
Results: Both patient and control group showed small-world topology in their SCNs. However, patients with PTSD exhibited abnormal global properties characterized by significantly decreased characteristic shortest path length and normalized characteristic shortest path length. Furthermore, the patient group showed enhanced nodal centralities predominately in salience network including bilateral anterior cingulate and pallidum, and hippocampus/parahippocamus gyrus, and decreased nodal centralities mainly in medial orbital part of superior frontal gyrus.
Limitations: The main limitation of this study is the small sample of PTSD patients, which may lead to decrease the statistic power. Consequently, this study should be considered an exploratory analysis.
Conclusions: These results are consistent with the notion that PTSD can be understood by investigating the dysfunction of large-scale, spatially distributed neural networks, and also provide structural evidences for further exploration of neurocircuitry models in PTSD.

1. Introduction

Post-traumatic stress disorder (PTSD) is a debilitating psychiatric disorder that develops in individuals who have been exposed to life-threatening metal traumas, including combat, childhood physical and sexual abuse, motor vehicle accidents, rape, natural disasters (Francati et al., 2007; Hughes and Shin, 2011). Among these traumas, road traffic accidents are one of the principal causes of PTSD (Chossegros et al., 2011), which has been extensively described since the 1980s (Malt, 1988). Patients with this disorder often suffer from one or more of the following symptoms: intrusive memories, flashbacks, hypervigilance, sleep disturbance, avoidance of traumatic stimuli, physiological hyperresponsivity, numbing of emotions, and social dysfunction (Francati et al., 2007; Hughes and Shin, 2011). Although the underlying pathophysiology of PTSD is still unclear, many theories that have been developed remain closely tied to the mechanisms from the preclinical findings.

Over the past two decades, PTSD was usually characterized by dysfunction of specific distributed brain regions, such as the amygdala with hyperactivation and the medial prefrontal cortex with hypoactivation (Carrion et al., 2009; Francati et al., 2007; Hayes et al., 2012; Hughes and Shin, 2011; Landre et al., 2012), which was then developed to a neurocircuitry model. Abundant evidences have demonstrated that the exaggerated activation of amygdala observed in PTSD has been speculated as a result of insufficient top-down regulation from the mPFC, as well as the

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anterior cingulate cortex (ACC), consequently leading to symptoms of hyperarousal and deficits in fear extinction (Francati et al., 2007; Hayes et al., 2012; Rabinak et al., 2011). However, the traditional neurocircuitry model of PTSD confronts challenges. One reason is because of the inconsistent results. Although there is agreement about the connection of mPFC and amygdala activity among neuroimaging studies (Francati et al., 2007; Rabinak et al., 2011), several findings pointed in different directions (Gilboa et al., 2004; Morey et al., 2008). Another reason, more importantly, is the limitation of this model in explaining the full range of heterogeneity of symptoms following a traumatic event. This model can account for fear-related symptoms in PTSD (Hayes et al., 2012), however, anxiety and fear may not be the central component in explaining PTSD symptomatology (Resick and Miller, 2009), suggesting that other emotions such as dysphoria are important in the development and maintenance of the disorder in addition to fear (Friedman et al., 2011). Recently, Patel et al. (2012) proposed that functional alterations of PTSD were involved in a triple network model that largely overlapped with the salience network (SN), central executive network (CEN), and default model network (DMN). However, heterogeneity was still observed within and across the three network models. The results depended on comparisons to non-trauma and trauma-exposed control groups (Patel et al., 2012). Interestingly, these previous studies only focus on discrete brain areas or local regions, it is largely unclear whether PTSD disrupts the global topological organization of large-scale whole brain network.

Numerous studies have suggested that graph theory framework can be used to character the topological organization of brain network (e.g. small-wordness, global efficiency) (Bullmore and Bassett, 2011; Gong et al., 2009; Micheloyannis et al., 2006; Sporns and Zwi, 2004). It is so powerful that it has been applied to many psychiatry disorders to detect pathology mechanisms and biological makers (Micheloyannis et al., 2006; Supekar et al., 2008; Zhang et al., 2011a). For example, evidences indicate that Alzheimer's disease is a disorder characterized by lower global efficiency between long-range discrete brain areas (Supekar et al., 2008). However, dysfunctions of brain network in PTSD have not been well understood. Only a few studies have investigated the functionally abnormal connections in PTSD (Lanius et al., 2010, 2005), which might be likely to contribute to the neural mechanism in this disorder. Furthermore, several studies have documented that functional interaction is greatly constrained by large-scale anatomical structure of human cerebral cortex (Greicius et al., 2009; Honey et al., 2009). And it is still unclear whether structural abnormalities underlie the alterations of neural function in PTSD. Therefore, it is necessary to study the structural substrate of distributed interactions among brain regions in PTSD for fully understanding the functional patterns such as activation and function connectivity. To test these structural alterations in PTSD, we utilized diffusion tensor imaging (DTI) tractography to investigate the topological organization of whole brain network.

DTI tractography is a noninvasive imaging technique to measure the white matter tracts between paired brain regions and is helpful for comprehension of the structural connection patterns of human brain (Basser et al., 2000). The DTI technique has been extensively used to investigate the structural alterations in human brain (Guo et al., 2012a, 2012b; Shu et al., 2011; Yan et al., 2011). However, there is little application in PTSD. Recently, several groups have applied the technique to reveal the PTSD-related changes in white matter integrity (Fani et al., 2012; Zhang et al., 2011b). These studies mainly focus on white matter connection in single brain region. The topological organization of whole brain structural connectivity network (SCN) in PTSD remains largely unknown.

In this study, we hypothesize that PTSD is characterized by disrupted topological organization of the SCN. To test the hypothesis, we collected structural data from 17 patients with PTSD in motor vehicle accident survivors and 15 normal controls without PTSD, and then employed DTI technique to reconstruct the SCN with nodes defined as 90 brain regions and edges defined as the mean fractional anisotropy between paired regions. Finally, graph theory and nonparametric test were applied to analysis topological properties and perform group comparisons of the topological metrics.

2. Materials and methods

2.1. Subjects

Seventeen PTSD patients (age: 30.76 ± 8.68) who had been involved in motor vehicle accident were recruited from Chongqing Southwest Hospital, Third Military Medical University. Diagnosis of PTSD was established with the Clinician-Administered PTSD Scale for DSM-IV (CAPS-DX) (Blake et al., 1995). Fifteen healthy controls (age: 25.60 ± 4.93) individually matched for age and gender were consecutively recruited. Inclusion criteria for all subjects were right-handedness, and an IQ > 80, as assessed with the Wechsler Intelligence Scale. Patients had no history of other Axis I psychiatric diagnoses other than depression on the Structured Clinical Interview for DSM-IV Axis I Disorders, whereas controls were free from Axis I diagnoses on the SCID (First, 1997). Exclusion criteria for both groups were contraindications for MRI and other neuropsychiatric disorders, such as schizophrenia, mental retardation, epilepsy, and head injury with loss of consciousness for more than 5 min. All PTSD patients had not taken psychotropic medication for at least 2 months.

This research was conducted in line with international ethic guidelines, and had been approved by the Ethics Committee of Third Military Medical University. All participants have signed the informed consent after receiving a complete description of the study. Demographic and clinical characteristics of these subjects can be seen in Table 1.

2.2. Image acquisition

All experiments were performed on a 3.0 T Siemens MRI scanner (Trio; Siemens Medical, Erlangen, Germany). Foam padding was used to minimize head motion of all subjects. T1-weighted images in the sagittal plane of all subjects were acquired using a 3D MPRAGE sequence (TR, 2000 ms; TE, 2.34 ms; flip angle, 7 deg; FOV, 256×256; voxel size, $1 \times 1 \times 1$ m^3; and slice thickness, 1 mm). Diffusion tensor imaging data was obtained using single shot echo planar imaging (EPI) sequence (TR, 9000 ms; TE, 106 ms; flip angle, 90 deg; FOV, 256×256; voxel size, $1 \times 1 \times 3$ mm^3; and slice thickness, 3 mm; acquisition plane, axial; 30 non-collinear diffusion weighting gradient direction [$b = 1000$ s/mm^2] and 1 additional image without diffusion weighting [$b = 0$ s/mm^2]).

2.3. Network construction

Nodes and edges are two basic elements of a network. To determine the nodes and edges of the brain network, we undertook the following steps, as previously suggested (Gong et al., 2009; Zhang et al., 2011c).

2.4. Network node definition

To determine the nodes of SCN in each subject, regions of interest were defined in native diffusion space (Gong et al., 2009). Accordingly, each individual T1-weighted image was first co-registered to