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Disrupted grey matter network morphology in pediatric posttraumatic stress disorder

Running Niu[a,1], Du Lei[a,b,1], Fuqin Chen[c], Ying Chen[a], Xueling Suo[a], Lingjiang Li[d], Su Lui[a], Xiaoqi Huang[a], John A. Sweeney[a,e], Qiyong Gong[a,f,*]

[a] Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu, Sichuan, China
[b] Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
[c] Department of Medical Information Engineering, School of Electrical Engineering and Information, Sichuan University, Chengdu, Sichuan, China
[d] Mental Health Institute, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China
[e] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH, USA
[f] Department of Psychology, School of Public Administration, Sichuan University, Chengdu, Sichuan, China

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ABSTRACT

Introduction: Disrupted topological organization of brain functional networks has been widely observed in posttraumatic stress disorder (PTSD). However, the topological organization of the brain grey matter (GM) network has not yet been investigated in pediatric PTSD who was more vulnerable to develop PTSD when exposed to stress.

Materials and methods: Twenty two pediatric PTSD patients and 22 matched trauma-exposed controls who survived a massive earthquake (8.0 magnitude on Richter scale) in Sichuan Province of western China in 2008 underwent structural brain imaging with MRI 8–15 months after the earthquake. Brain networks were constructed based on the morphological similarity of GM across regions, and analyzed using graph theory approaches. Nonparametric permutation testing was performed to assess group differences in each topological metric.

Results: Compared with controls, brain networks of PTSD patients were characterized by decreased characteristic path length ($P = 0.0060$) and increased clustering coefficient ($P = 0.0227$), global efficiency ($P = 0.0085$) and local efficiency ($P = 0.0024$). Locally, patients with PTSD exhibited increased centrality in nodes of the default-mode (DMN), central executive (CEN) and salience networks (SN), involving medial prefrontal (mPFC), parietal, anterior cingulate (ACC), occipital and olfactory cortex and hippocampus.

Conclusions: Our analyses of topological brain networks in children with PTSD indicate a significantly more segregated and integrated organization. The associations and disassociations between these grey matter findings and white matter (WM) and functional changes previously reported in this sample may be important for diagnostic purposes and understanding the brain maturational effects of pediatric PTSD.

1. Introduction

Post-traumatic stress disorder (PTSD) can develop following exposure to extremely traumatic life events such as violence, combat, life-threatening accidents or natural disasters. PTSD is the only psychiatric disorder with known cause, and is characterized by a constellation of symptoms including re-experience, avoidance, and hyperarousal (Association, A.P., 2013). Its lifetime prevalence is 6.8% of general adult populations (Kessler et al., 2005) and 5% in adolescents (Merikangas et al., 2010), and it occurs in 24% of individuals after particularly serious stressors such as occur in earthquake survivors (Dai et al., 2016). The comorbidities of PTSD can include substance abuse, mood and anxiety disorders, impulsive or dangerous behavior and self-harm. PTSD is also associated with considerable medical comorbidities, including chronic pain and inflammation, cardiometabolic disorders and heightened risk of dementia. In children, the functional disability of PTSD can persist for years into adulthood, with long-term influence on social and brain development (Lamberg, 2001).

Both functional and structural brain alterations in PTSD have been reported (Chen et al., 2013; Li et al., 2016; Lui et al., 2009; Cisler et al.,

* Corresponding author at: Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, No. 37 Guo Xue Xiang, Chengdu, Sichuan 610041, China.
E-mail address: qiyonggong@hmrrc.org.cn (Q. Gong).
[1] Running Niu and Du Lei contributed equally to this work.

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2016a), but their neurobiology and pathogenesis remain unclear (Liberzon and Abelson, 2016). In recent years, studying the brain connectome using graph theory approaches has emerged as an important strategy for detecting alterations of brain networks in neuropsychiatric disorders (Sporns et al., 2005). The primate brain has been shown to be topologically organized in a small-world network which has higher segregation and integration functions than a random and regular network (He et al., 2007; Salvador et al., 2005; Stam, 2004). Disruption of this topological organization has been associated with epilepsy (Bernhardt et al., 2016; Bernhardt et al., 2015; Sethi et al., 2016), Alzheimer's disease (He et al., 2008; Stam et al., 2009; Tijms et al., 2013a), schizophrenia (Alexander-Bloch et al., 2013a; Li et al., 2012; van den Heuvel et al., 2010), and major depression (Zhang et al., 2011; Wang et al., 2016; Guo et al., 2012). Compared with healthy and trauma-exposed populations, patients with PTSD exhibited altered brain network organizations in previous resting state fMRI studies (Spielberg et al., 2015; Kennis et al., 2016; Cisler et al., 2016b). Our study of adult PTSD patients showed that functional networks demonstrated a shift toward “small-worldization” indicated by higher both segregation and integration (Lei et al., 2015a). A previous study of PTSD using diffusion-tensor imaging (DTI) showed that WM networks shifts toward “randomization” of network organization with only higher integration (Long et al., 2013).

Compared to studies of resting state fMRI and diffusion tensor imaging, there are few studies using grey matter to examine brain structural networks in patients with PTSD. As with fMRI and DTI data, grey matter structural MRI can also be used to delineate whole-brain connectivity patterns by calculating interregional morphological associations (He et al., 2007; Alexander-Bloch et al., 2013b) based on the structural covariance of grey matter volume and cortical thickness. This approach has been used to examine connectome organization in healthy individuals (He et al., 2007; Fan et al., 2011; Chen et al., 2008) and in patients with psychiatric disorders (He et al., 2008; Bassett et al., 2008; Singh et al., 2013). Only two studies have investigated GM network organizations of PTSD, both with adult participants. These studies demonstrated a loss of small world organization and characteristics of higher segregation and integration with a shorter path length and higher clustering (Mueller et al., 2015; Qi et al., 2017).

A new method proposed by Tijms and colleagues has been developed to statistically describe grey matter networks in individual subjects using T1-weighted MRI scans (Tijms et al., 2012). In this method, networks are constructed with nodes representing small brain regions whose connections are computed by evaluating intracortical similarities in grey matter morphology. This method has been successfully applied to study Alzheimer's disease (Tijms et al., 2013a; Tijms et al., 2016; Tijms et al., 2013b; Tijms et al., 2014) and individuals at risk for schizophrenia (Tijms et al., 2015). Batalle and colleagues (Batalle et al., 2013) extended this method to allow normalization of grey matter networks so that each person has the same network size (90 nodes). This method has advantages for comparative analyses such as in patient-control comparisons. No studies have applied this approach in PTSD.

Children are thought to be more vulnerable to developing PTSD following trauma than adults (Fletcher, 1996). To our knowledge, only two studies from our group investigated brain topological organization in pediatric PTSD. These studies demonstrated disruption of brain functional and WM networks using resting-state MRI (rs-MRI) and diffusion-tensor imaging (DTI) (Suo et al., 2017; Suo et al., 2015). The segregation function was increased in functional networks and decreased in WM networks, while the integration function of WM networks was decreased. Whether there are changes in the GM networks in children with PTSD and how such alterations may related to symptom severity and these previous findings using other imaging modalities is unknown.

The purpose of this study was to investigate the topological organization of brain GM networks in children who experienced a single traumatic event. We recruited 22 children with PTSD and 22 trauma-exposed healthy control subjects followed 1 year after the 8.0 magnitude Wenchuan earthquake in south-west China. After constructing individual morphological cortical networks, graph-based models were employed to characterize grey matter topology for each study participant. Given previous evidence of higher segregation function in resting-state fMRI networks and lower integration function of WM networks in pediatric PTSD, we hypothesized that (i) similar disruptions would also characterize the present grey matter networks in our pediatric sample. We also hypothesized (ii) lower nodal betweeness, degree and efficiency in our grey matter networks based on previous findings of two adult PTSD studies of grey matter networks (Mueller et al., 2015; Qi et al., 2017). Finally, (iii) we predicted relationships of network disruption with clinical severity and age.

2. Materials and methods

2.1. Participants

The participants who survived a massive earthquake (8.0 magnitude on Richter scale) in Sichuan Province of western China in 2008 were recruited in the town of Hanwang and nearby areas of Beichuan County, which are about 80 km and 113 km from the epicenter respectively. This study was approved by the local research ethics committee. Each child's guardian provided written informed consent and children provided assent prior to participation.

A large-scale PTSD survey was conducted by Y.C., S.L and X.H. among 4200 survivors 8–15 months after the earthquake. From that sample we selected participants who (i) physically experienced the earthquake, (ii) personally witnessed death, serious injury or the collapse of buildings, (iii)had no diagnosis of PTSD prior to the earthquake, (iv) were younger than 18 years of age, and (v) had an intelligence quotient > 80.

The parent form of the PTSD Checklist (PCL) was used to screen potential subjects (Weathers et al., 1994) and the Clinician Administered PTSD Scale (CAPS) was completed when PCL scores were ≥35 (Blake et al., 1995). The subjects were considered eligible for inclusion in the PTSD group who had a CAPS score of 50 points or greater. Those with PCL scores < 30 were considered study eligible as non-PTSD controls who also experienced the stress of the earthquake (Jin et al., 2014). This yielded a total of 161 potential PTSD patients and 99 non-PTSD controls. In these subjects, the presence/absence of PTSD and psychiatric comorbidities were confirmed by an experienced psychiatrist (L.L.) using the Structured Clinical Interview for DSM-IV (SCID; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (First et al., 1997)). Both the children and their parents were interviewed and the information from parents was combined by the psychiatrist to support diagnosis.

Exclusion criteria were: (i) history of depression, bipolar or psychotic disorder, or neurologic disorder (n = 42), (ii) contraindication to MR imaging (n = 30), (iii) treatment with psychiatric medications within two months before recruitment for MRI scanning (n = 24), (iv) unavailability of key data (n = 12); (v) left handedness (n = 10); (vi) CAPS score > 35 but < 50 (n = 8) (Jin et al., 2014), and (vii) history of brain injury (n = 7). Six patients and 4 controls were excluded because of excessive head motion during 3D T1 MRI scanning.

With these exclusions to obtain a relatively homogeneous sample, we recruited 22 drug-free first-episode patients with PTSD and a demographically matched group of 22 trauma exposed subjects who did not develop PTSD for the present study. The two groups had similar demographic characteristics, lifestyles, and earthquake experiences (Table 1). Selecting healthy individuals who also experienced the earthquake as a comparison group was done to control for stress exposure. Thus, our study was designed to identify factors associated with PTSD independent of stress exposure effects.