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Disrupted topological organization in the whole-brain functional network of trauma-exposed firefighters: A preliminary study

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A B S T R A C T

Given that partial posttraumatic stress disorder (pPTSD) may be a specific risk factor for the development of posttraumatic stress disorder (PTSD), it is important to understand the neurobiology of pPTSD. However, there are few extant studies in this domain. Using resting-state functional magnetic resonance imaging (rs-fMRI) and a graph theoretical approach, we compared the topological organization of the whole-brain functional network in trauma-exposed firefighters with pPTSD (pPTSD group, $n=9$) with those without pPTSD (PC group, $n=8$) and non-traumatized healthy controls (HC group, $n=11$). We also examined changes in the network topology of five individuals with pPTSD before and after eye movement desensitization and reprocessing (EMDR) therapy. Individuals with pPTSD exhibited altered global properties, including a reduction in values of a normalized clustering coefficient, normalized local efficiency, and small-worldness. We also observed altered local properties, particularly in the association cortex, including the temporal and parietal cortices, across groups. These disruptive global and local network properties presented in pPTSD before treatment were ameliorated after treatment. Our preliminary results suggest that subthreshold manifestation of PTSD may be due to a disruption in the optimal balance in the functional brain networks and that this disruption can be ameliorated by psychotherapy.

1. Introduction

Exposure to traumatic events can lead to brain abnormalities and posttraumatic stress disorder (PTSD). Specific occupational groups, such as firefighters, frequently experience extremely stressful (traumatic) events in the line of duty that can increase the risk for PTSD symptoms (Beaton and Murphy, 1993; Corneil et al., 1999). According to literature (Bryant and Harvey, 1995; Wagner et al., 1998; Corneil et al., 1999), the prevalence rate of PTSD is two times greater in firefighters (18–37%) than general population (approximately 7–9%). However, relative to other traumatized individuals (e.g., disaster survivors), firefighters have been understudied, even though this population may be critical for our understanding of brain changes that occur in response to work-related traumatic stressors.

There is an increasing awareness that partial PTSD (pPTSD) or subthreshold PTSD (i.e., symptoms that fail to satisfy the full diagnostic criteria) exists (Weiss et al., 1992). Studies have demonstrated that pPTSD is about as prevalent as full PTSD (approximately 6.6–9.8%) and that it results in functional impairments as severe as those associated with full PTSD (Stein et al., 1997; Pietrzak et al., 2011; Mitchell et al., 2012; Schnurr, 2014). Individuals with pPTSD can be regarded as at-risk individuals who are in the prodromal phase of PTSD or as resilient people who have avoided development of the full disorder (Schnurr, 2014).

Neuroimaging studies have revealed a variety of abnormalities in brain structure (Li et al., 2014; Meng et al., 2014; O'Doherty et al., 2015) and function (Etkin and Wager, 2007; Hughes and Shin, 2011) in patients with PTSD, particularly in the hippocampus/parahippocampal gyrus (PHG), amygdala, medial prefrontal cortex, anterior cingulate cortex, insula, and occipital cortex. Further studies have demonstrated that traumatic stress itself may have a substantial impact on brain structure and function (Dannlowski et al., 2012). Taken together, brain changes may exist on a continuum, ranging from those found in trauma-exposed individuals without PTSD to those found in patients with full PTSD. However, the brain alterations associated with pPTSD remain unclear and, therefore, require further investigation. Given that pPTSD may reflect a risk factor for the development of PTSD, it is important to improve our understanding of this phenomenon.

Different psychological interventions have been used for the

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treatment of PTSD, including exposure therapy, cognitive therapy, psychodynamic therapy, and eye movement desensitization and reprocessing (EMDR) (refer to Bisson et al. (2013) for a detailed explanation for each therapy). EMDR is an evidence-based effective psychotherapy and currently recommended as the treatment of choice for trauma by international guidelines (Bradley et al., 2005; Ponniah and Hollon, 2009; Bisson et al., 2013; World Health Organization, 2013; Chen et al., 2014; Cusack et al., 2016). Like cognitive behavioral therapy (CBT) with a trauma focus, EMDR therapy aims to reduce subjective distress and strengthen adaptive cognitions related to the traumatic event. However, unlike CBT with a trauma focus, EMDR has the merit that it does not involve (i) detailed descriptions of the event, (ii) direct challenging of beliefs, (iii) extended exposure, or (iv) homework. (World Health Organization, 2013). During EMDR therapy, individuals suffering from PTSD attend to their traumatic memory while simultaneously focusing on an external stimulus, known as bilateral stimulation that is most commonly in the form of eye movements (Shapiro, 2001). Recently, several studies have examined neurobiological mechanism for the effect of EMDR on PTSD (Bergmann, 2010; Thomaes et al., 2014). These studies have showed that functional brain abnormalities in patients normalize with the improvement of symptoms following EMDR treatment (Pagani et al., 2012, 2015)

Graph theoretical analysis (GTA) of resting-state fMRI (rs-fMRI) has been recently used to measure the topological organization of the intrinsic functional brain networks under normal and psychiatric conditions. Many GTA studies with normal subjects have consistently demonstrated that the human brain can be conceptualized as a small-world network structure characterized by highly segregated (i.e., high clustering coefficient) and integrative (i.e., short path length) connectivity patterns in the large-scale brain system (Bullmore and Sporns, 2009; Wang et al., 2010). Further studies have revealed the disruption of small-world properties in the functional brain networks of individuals with diverse neuropsychiatric disorders, including schizophrenia (Lynall et al., 2010), major depressive disorder (MDD; Zhang et al., 2011), and obsessive–compulsive disorder (OCD; Shin et al., 2014). The heterogeneous topological changes observed in patients with different disorders can be regarded as disturbances in the optimal balance between the functional segregation and integration within the networks (Watts and Strogatz, 1998). Recently, several studies on PTSD have reported abnormalities in the small-world properties of brain networks derived from different modalities, including resting-state functional network (Lei et al., 2015; Suo et al., 2015), structural network based on diffusion tensor imaging (DTI) tractography (Long et al., 2013), and structural covariance network based on gray matter volume/thickness (Mueller et al., 2015). However, no study has investigated whether changes in the topology of brain networks exist in pPTSD.

To overcome all the aforementioned issues, we used GTA of rs-fMRI to investigate the topological organization of the whole-brain functional network of firefighters who suffer from pPTSD. Based on previous findings in patients with PTSD, we hypothesized that individuals with pPTSD show altered small-world properties of the whole-brain functional brain network and that these disruptions would be ameliorated after psychotherapy. To test our hypotheses, we selected small-world parameters, including clustering coefficient and characteristic path length, to compute small-worldness measured by the ratio between these two metrics and global and local efficiency to better quantify the level of functional integration and segregation in the network (Latora and Machiori, 2001; Crucitti et al., 2003). We also investigated betweenness centrality (BC) as a nodal network metric, which indicates the relative importance of a node in the network. Nodes with a high BC are the ones that act as bridges between other nodes and thus can be regarded as hubs in the network. Specifically, we compared such diverse measures of network topology in trauma-exposed firefighters with and without pPTSD and non-traumatized healthy controls to distinguish disorder-related brain alterations from stress-related ones. We also examined whether EMDR can improve the disruptive network topology observed in pPTSD before treatment.

2. Methods

2.1. Participants

We recruited 116 firefighters from fire stations in Seoul, South Korea who volunteered to participate in this study. Participants underwent comprehensive medical and psychiatric interviews performed by trained psychiatrists. Of this initial pool, 67 male firefighters were enrolled in the study. Then, PTSD diagnosis was performed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P); individuals with pPTSD were defined as those who presented with fewer than the requisite number of DSM-IV criterion B (re-experiencing) or C (avoidance/numbing) or D (hyperarousal) symptoms required for full PTSD but who experienced at least one symptom in each category (Blanchard et al., 1995; Stein et al., 1997). Fifteen of 67 firefighters were diagnosed with pPTSD, and the remainder was identified as the trauma-exposed group without pPTSD (i.e., the patient control [PC] group). Of these, 10 in the pPTSD and eight in the PC group agreed to participate in this imaging study. Six of the 10 individuals with pPTSD were re-scanned following psychotherapy. We also recruited 12 healthy controls (HC) who were matched for age, gender, and education with the other groups and who served as a general non-traumatized group. The exclusion criteria for all groups were as follows: 1) history of traumatic brain injury, 2) presence of comorbid medical conditions, 3) history of psychiatric disorders (e.g., psychotic or mood disorders), 4) history of substance abuse (including alcohol-related disorders), 5) current use of psychotropics, and 6) life-threatening conditions. Two subjects (1 HC and 1 with pPTSD) were excluded from the analysis because of technical problems. Fig. 1 shows a flow chart of the recruiting process for each group. The following numbers of subjects were involved in each analysis: cross-sectional analysis: 11 HC, 8 PC, and 9 with pPTSD; longitudinal analysis, 5 with pPTSD before and after treatment. The demographic and clinical characteristics of each group are provided in Table 1. This study was approved by the Institutional Review Board of the Seoul Metropolitan Eunpyeong Hospital. All participants provided signed informed consent forms after receiving a complete description of the study.

2.2. Symptom measures

All participants were assessed with both the Impact of Event Scale-Revised (IES-R; Weiss and Marmar, 1997) and Life Events Checklist (LEC; Blake et al., 1990). The IES-R was used to assess subjective distress as measured by intrusive, avoidance, and hyperarousal symptoms that arise from traumatic experiences. The LEC was used to screen for potentially traumatic events over the life course. A score was obtained for the total number of directly experienced life events (DEL). Individuals defined as suffering from pPTSD were administered the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1990). The CAPS is a semi-structured interview and represents the gold standard for PTSD diagnosis and for measuring symptom severity. Particularly, both IES-R and CAPS were administered before and after EMDR as outcome measures.