Neural network properties of combat-related PTSD

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Introduction

Posttraumatic stress disorder (PTSD) is an anxiety disorder developed after traumatic experience with typical symptoms such as re-experiencing, hyper-arousal and avoidance [1]. Previous neuroimaging studies of PTSD have focused on the abnormal structures and functionality of a few individual brain regions [2,3], but have not paid much attention on the connectivity between these structures. Overcoming the limitation of traditional seed-based functional connectivity analysis, the present study used graph theory based analysis approaches [4] to provide an overview of the connectivity in the whole neural network, as well as the properties of the neural network, with resting state fMRI data from trauma-exposed subjects with and without PTSD.

Methods

Volunteers were recruited from community as well as VA mental health clinic. General inclusion criteria include being a US veteran of OIF/OEF, between the age of 20 and 60 years, and being able to understand the protocol and willing to provide written informed consent, and exclusion criteria include substance dependence, life time history of psychiatric disorder, history of close-head injury with loss of consciousness over 30 minutes, or with any metal in body including a pacemaker. Based on clinical interview, criteria for PTSD+ were war-zone exposure related PTSD symptoms of at least 3 month duration as indexed by the Clinician Administered PTSD Scale (CAPS) [5]. The criteria for PTSD- were warzone exposure and no history of PTSD symptoms over lifetime that was no less than 20 on the CAPS. One hundred and one male veterans, with forty nine PTSD+ and fifty two PTSD-, were included in this cohort of study, with the two groups matched on age gender and ethnicity. Images were acquired on a SIEMENS 3T Trio whole-body scanner (Siemens AG, Erlangen Germany) using a 12 channel array coil. Anatomical images were acquired with T1-weighted Magnetization Prepared RApid Gradient Echo (MP-RAGE) sequence (iPAT factor = 2) with phase-encoding in the sagittal plane, with TE/TI/TR=2.98/900/2300 ms, 256×240 matrix, 256×240 mm^2 field-of-view (FOV), flip angle=9; 192 slices 1 mm thick 3D-MRI were obtained from each subject. Resting state fMRI was obtained using an EPI sequence (TR/TE = 2000/29 ms, flip angle = 90◦), 64×64 matrix, pixel size 3.125×3.125mm^2. A total of 200 volumes with each volume containing 32 contiguous axial slices at 3.5 mm thickness (without gaps) covering the whole cortex, were acquired from each subject. Throughout the scanning, subjects were instructed to lay in the scanner supine, relaxed, stay awake, remain still and keep their eyes open.

After preprocessing, whole brain neural network was constructed via pair-wise functional connectivity among regions based on parcellation [6] using the template for automatic anatomical labeling (AAL) to provide 90 regions of interest. For the purpose of group average, the correlation coefficients (r-scores) were transformed to Z scores, and averaged for each group (Fig 1. A,B). Then various properties of the graphs was analyzed, including degree, cluster coefficient, global efficiency and local efficiency [4] (Fig. 1. C, D). Furthermore, a hub index were calculated based on a recently proposed protocol [7], as illustrated in Figure 1. E, suppose each colored circle represents a detected functional cluster[7], then node "a" can be considered as a "hub" since it participates in multiple functional clusters whereas node "b" cannot although with comparable amount of connections as node "a", the hub index is a continuous value reflects such concept. The PTSD+ group demonstrated a pattern of less distinguishable hubs (Fig 1.F).

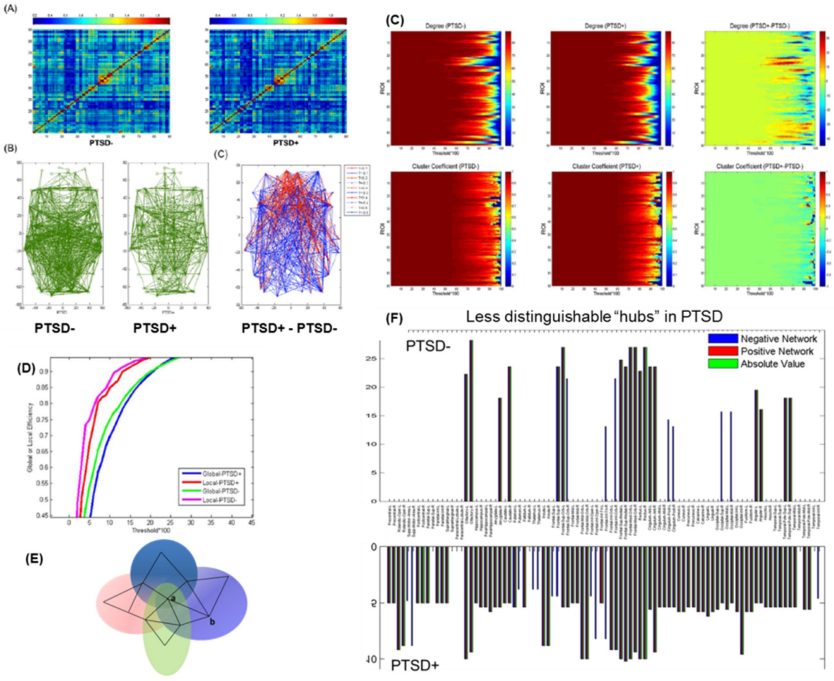

Figure 1: Neural network analysis of PTSD. (A) Raw pairwise functional connectivity matrix of the 90 ROIs with AAL parcellation. (B) Visualization of the neural network of each individual group as well as group difference. (C) The network properties, "degree" and cluster coefficient of each individual group as well as group difference. (D) The global and local efficiency of the neural network of each group. (E) Illustration of the definition of "hubs" based on overlapping functional clusters. (F) Distribution of the "hub" index across the 90 ROIs in each group.

Results & Discussion

The functional connectivity matrix for each group was plotted as demonstration of raw data, as well as the corresponding graphs. Direct observations suggest that the neural network of the PTSD+ group has a large amount of connections with weaker connectivity compared to the network of the PTSD- group (Fig1.A) Analysis about the distribution of cluster coefficient at each brain region demonstrated significantly decreased cluster coefficients at the bilateral orbital frontal cortex and the left inferior temporal lobe ($p < 0.05$, corrected). No significant differences were found in degree distribution. Analysis about the global efficiency and the local efficiency of the two groups revealed that the neural network of the PTSD+ group tend to have lower global and local efficiency compared to the PTSD- group, the difference did not reach statistical difference in group statistics, although the group differences were remarkably high from the average graphs of each group (up to -0.24 for local efficiency and up to -0.12 in global efficiency). No significant differences were found in small world index, or characteristic path length. The hub regions in the neural network of the PTSD+ group were less distinguishable and weaker compared to those of the PTSD- group.

Network analysis is a relatively new approach and there has not been a previous network study on PTSD, although it has been used to study other mental disorders such as Alzheimer's disease (AD), schizophrenia, attention deficit hyperactivity disorder, epilepsy, as well as severe traumatic brain injury (TBI), e.g., the changes of neural network properties of six subjects with severe TBI, such as a significant reduction of global and local efficiency as a function of the length of the time interval post injury [8]. Distribution of "hub" regions in the neural network is also an important aspect of the network property. A previous study investigated the distribution of "hub" regions in AD, and further revealed high amyloid deposition in the hub regions, supporting the hypothesis that while hubs act as critical stations for information processing their high activity also augment the underlying pathological cascade in AD[9]. The present study suggests that there are less distinguishable hubs in the neural network of PTSD+ group, which indicate that the network of PTSD patients is nosier than that of the controls. However it is worth further investigation whether such property could progress during the course of treatment and recovery. In summary the present study investigated the properties of the neural network of PTSD patients. Such approach is helpful in overcoming the limitation of traditional approaches which "miss the forest for the trees" and provides important information about the global network properties.

Reference

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