Functional connectivity with the fear circuitry in combat-related PTSD

Leslie Yan[1], Mariana Lazar[1], Clare Henn-Haase[1], and Charles Marmar[1]
[1]*New York University, New York, NY, United States*

Introduction

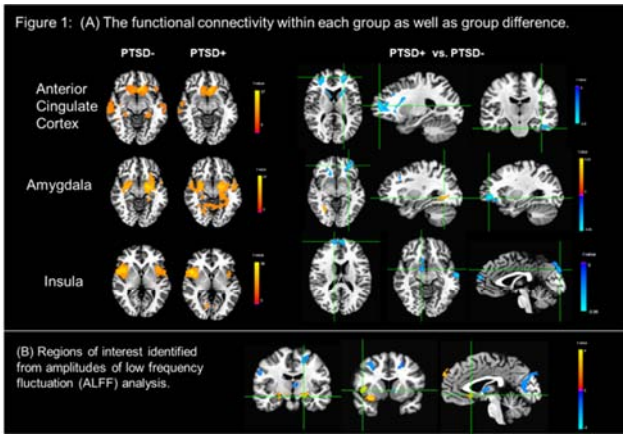
Posttraumatic stress disorder (PTSD) is an anxiety disorder following traumatic experience with typical symptoms such as re-experiencing, hyper-arousal and avoidance [1]. Previous studies with neuroimaging and animal models have identified several brain structures of the "fear circuitry" to play critical roles in the neural mechanism of PTSD, including the amygdala, the anterior cingulate cortex and the insula; these structures are shown to be "hyper-responsive" in previous task-based neuroimaging studies during symptom provocation conditions [2]. However the neural connectivity between these structures and other neural systems has not yet been systematically investigated, therefore the present study used resting state fMRI to study the functional connectivity with the above mentioned structures as seeds in PTSD subjects and controls.

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) [3]. 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, the average signal from each of the following seeds: the anterior cingulate cortex, the right amygdala and the right anterior insula as identified in the group difference of amplitude of low frequency fluctuation (ALFF) analysis [4], was obtained from the normalized data of each subject to be used as a reference for FC analysis on that subject. For each of the seeds, Pearson correlation was used to measure temporal synchronization between the reference signal and the signal in every voxel in the preprocessed data in each subject, generating an R-map for each subject. The fisher r-z transformation was conducted to transform the *r* scores of each voxel into z scores, generating a Z-map for each subject. An independent two-sample t-test was conducted on the Z maps of the two groups with 3dttest++ command in AFNI. Age, education level, ethnicity were used as covariates. Clusters showing significant group differences were identified with a threshold of $p < 0.05$ (FDR corrected) and a minimum cluster size of 810 mm^3. Pearson correlations were conducted between regional Z values (from the significant clusters) and clinical scales.

Results & Discussion

Results demonstrated that amygdala of the PTSD+ group had significantly lower FC between the amygdala and the medial prefrontal cortex, but higher FC with the parahippocampal gyrus. The strength of amygdala-frontal FC was positively correlated with scores of PDEQ, and the strength of amgydala-parahippocampal FC was positively correlated with scores of early trauma inventory (ETI) ($p < 0.05$ corrected). Compared to the PTSD- group, the PTSD+ group showed decreased functional connectivity with the anterior cingulate cortex, particularly demonstrated at the superior frontal cortex, inferior frontal gyrus, the middle temporal cortex and the cuneus. With the right anterior insula, the PTSD+ group also showed significantly lower functional connectivity with the medial globus pallidus, the superior & middle frontal cortex, the precuneus, the middle temporal cortex, and the paracentral lobe. The FC between the right anterior insula and the precuneus had significant positive correlation with the amount of re-experiencing symptoms measured by CAPS subscale ($p < 0.05$ corrected).



Previous studies with animal models have suggested decreased prefrontal inhibition on the fear circuitry plays an important role in PTSD pathology [5], which is supported by findings in the present study which demonstrated reduced communication between the fear circuitry and the prefrontal cortex. A previous resting state fMRI study also reported reduced amygdala-frontal FC in combat veterans with PTSD compared to combat veterans without PTSD [6], although another similar study did not find significant group differences in amygdala-frontal FC [7].In terms of association with clinical symptoms, previous studies did not reveal any significant correlations between amygdala functional connectivity and symptoms [6, 7], but the present study revealed associations with depression, early life trauma and peritraumatic dissociative symptoms. It is worth noting that the amygdala-parahippocampal gyrus FC had significant correlation with the early life trauma, which is consistent with existing knowledge about the endorsement of amygdala circuitry in the long term impact of early life trauma [8]. The amygdala-frontal FC showed significant correlation with peritraumatic dissociative symptoms, which could be related to the improper memory processing during trauma that constitutes a strong predictor of PTSD symptoms [9].

The functional connectivity of the anterior cingulate cortex and insula has not been investigated in the PTSD literature. In terms of functional connectivity of the anterior cingulate cortex, the PTSD+ group showed decreased functional connectivity at lateral prefrontal cortex and temporal cortex. The lateral prefrontal cortex has been known to play a critical role in the integration of emotion and cognition [10], the middle temporal cortex has been known to be important for attention control [11], and the anterior cingualte cortex has also been known to be an interface between emotion, motor and cognition [12], and plays an important role in conflict monitoring [13], thus the decreased functional connectivity between the lateral prefrontal cortex and the anterior cingulate cortex could indicate dissociated coordination between these structures which could contribute to the chaotic emotion and cognitive processing in PTSD patients. In terms of insular functional connectivity, the PTSD+ group showed decreased functional connectivity with cores of the default mode network, which endorsed a substantial amount of depression symptoms. Such pattern relates to the importance of the default mode network in emotion regulation and proper self-referential processing [14], in additional to the traditionally conceptualized frontal inhibition. With depression as an important aspect of psychopathology of PTSD, results from the present study also suggest that the insular network could be its underlying neural substrates.

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