Amplitude of low frequency fluctuations and functional connectivity in resting state fMRI among PTSD

Xiaodan YAN1,2, Mariana Lazar1, Victoria Cressman1, Leslie Prichep3, Clare Henn-Haase2, Irene Lee2, Rachel Yehuda1, Thomas Neylan1, Daniel Sodickson1, and Charles Marmar2

1Radiology, New York University, New York, NY, United States; 2Department of Psychiatry, New York University, New York, NY, United States; 3Department of Psychiatry, Manhattan VA Medical Center, New York, NY, United States; 4Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, United States

Introduction
Posttraumatic stress disorder (PTSD) is an anxiety disorder that can develop following a traumatic experience that typically involves threat of injury or death. PTSD symptoms are characterized by constant re-experiencing of traumatic memory, hyperarousal, avoidance and emotional numbing[1]. Blood oxygenation level dependent functional MRI (BOLD-fMRI), is helpful in revealing PTSD associated neuropathology [2]; however, findings from these task-based studies have been inconsistent due to their different targeted response variables[2]. The present study used resting state fMRI to study the spontaneous activity and functional connectivity on combat-related PTSD.

Methods & Results
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 closed-head injury with loss of consciousness over 10 minutes, or any with metal in body including a pacemaker. After the initial screening, volunteers were administered a clinical interview. Criteria for PTSD+ was war-zone exposure and 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. Thirty-eight male veterans, with 19 PTSD+ and 19 PTSD-, were included in this cohort of study. The two groups were matched on age, gender, ethnicity, and education levels (Table 1). Several self-report questionnaires were administered including the PTSD Checklist (PCL) [4], Beck Depression Index (BDI)[5], Emotion Regulation Scale (ERS)[6] and Peritraumatic Dissociative Experiences Questionnaire (PDEQ)[7].

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 Magnatization Prepared Rapid Gradient Echo (MP-RAGE) sequence (IPAT factor = 2) with phase-encoding in the sagittal plane, with TE/TI/TR=2.98/90/2000 ms, 256X240 matrix, 256X240 mm field-of-view (FOV), flip angle=90, 192 slices 1 mm thick. 3D-MRI was obtained from each subject. Rs-fMRI was obtained using an EPI sequence (TR/TE=2900/29 ms, flip angle=90°, 64X64 matrix, pixel size 3.125X3.125mm². 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. Amplitudes of low frequency fluctuation (ALFF) was processed on rs-fMRI data with a published protocol [8]. Individual ALFF maps were normalized to the Talairach and Tournoux space for each subject using a non-linear transformation. An independent two-sample t-test was conducted on the ALFF maps of the two groups. Clusters showing significant group differences were identified with a threshold of p<0.05 (FWE corrected) and a minimum cluster size of 800 mm³ (Figure 1, Table 2). Among the PTSD+ only, Pearson correlation analysis was conducted between regional ALFF values (from the significant clusters) and clinical scales. Bonferroni correction was applied to address the issue of multiple comparisons when determining significance. Significant clusters (Table 2) were used as ROIs for FC analysis. The average preprocessed BOLD signal was extracted from the ROIs and pairwise Pearson correlation coefficients were obtained in each individual subject, with a z score obtained from each pair of ROIs. The z scores were transformed according to the Fisher transformation (Fisher 1915). The z scores were averaged within each group for the FCs between each pair of ROI-s. The z scores were visualized in the form of color-coded matrices (Figure 2.A); based on the Fisher transformation, in the case of self-correlation, the r score which equals 1 will be transformed into a z score of infinity. Thus, for the purpose of visualization, these z scores in the diagonal matrices were set to 0 manually. For each pair of ROI, a two-sample t-test was conducted, with a t-value and p-value obtained for each pair of ROI-s, the p values were used to represent the levels of significance in Figure 2.B. Bonferroni correction was applied here to address the multiple comparison issue with multiple pairs of correlation giving rise to the corrected p-value of 2.3E-15.

Discussion & Conclusion
Major findings in the present study include decreased baseline activity in the default mode network (e.g., PCC & precuneus) [9] and increased baseline activity at some limbic structures (e.g., ACC, Insula)(Figure 2.A), in addition to decreased spontaneous activity (ALFF) of dorsal frontotemporal cortex, PCC and precuneus may relate to their deficiency in self-referential processing [10]. Adaptive function was observed at the precuneus through its positive correlation with ERS (Figure 3.F). Hyperactivity at ventral frontal cortex, insula and vACC may relate to high spontaneous activity in the emotion system among PTSD+ at resting state. Thalamic hypoactivity which was associated with re-experiencing symptoms (Figure 3.C) and thalamo-cortical arhythmia supports a hypothesis brought up by Llinas about thalamic-mediated cognitive binding deficiency for PTSD neuropathology[11].

Reference