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

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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, hyper-arousal, 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 close-head injury with loss of consciousness over 10 minutes, or with any 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 d uration 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].

Table 1: Demographic characteristics and psychometric ratings of study participants, presented in the form of "mean (SD)" for continuous variables or "frequency" for discrete variables.

		PTSD+	PTSD-	*p*-value
N		19	19	
Age		32.32 (7.69)	29.79 (7.93)	0.3256
Gender				1
	Female	0	0	
	Male	19	19	
Education				1
	High school diploma	6	6	
	Two year college/AA degree	6	6	
	Four year college/Batchecholar	7	7	
Ethnicity				0.883
	Black	3	3	
	White	3	4	
	Hispanic	12	11	
	Other	1	2	
BDI		21.05 (7.57)	4.79 (5.29)	$p < 0.001$
ERS		24.42 (7.30)	38.05 (7.43)	$p < 0.001$
PDEQ		1.62 (0.90)	0.53 (0.74)	$p < 0.001$
PCL re-experience		16.68 (3.59)	5.95 (1.51)	$p < 0.001$
PCL avoidance		22.74 (4.95)	9.79 (2.55)	$p < 0.001$
PCL hyperarousal		18.68 (3.67)	9.11 (4.07)	$p < 0.001$
PCL total		58.11 (9.25)	24.84 (6.81)	$p < 0.001$

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. Rs-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. 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 mm^3(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 ROI-s 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 an r score obtained from each pair of ROI-s. The r scores were transformed into z scores with the Fisher transformation (Fisher 1915). The z scores were averaged within each group for the FC-s between each pair of ROI-s. The z scores were visualized in the form of color-coded matrix (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 infinite. Thus, for the purpose of visualization, these z scores in the diagonal of matrixes 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 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.

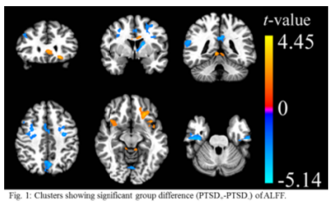

Fig. 1: Clusters showing significant group difference (PTSD+/PTSD-) of ALFF.

Area	Volume (mm^3)	BA		Talairach (CM) x	y	z	*t* value (peak)
Precuneus	12762	31	L&R	4.9	69.9	23.2	-5.14
Dorsal frontal cortex	5550	9	R	-45	-22	33	-4.13
Thalamus	1644		L	11.5	4	12.9	-3.94
Dorsal frontal cortex	4959	6	L	26	3.3	42.2	-3.91
Superior temporal cortex	1265	22	R	-54	49	17	-3.85
Fusiform cortex	1653	20	R	-47	17	-24	-3.76
Fusiform cortex	1214	20	L	53	17	-23	-3.66
Posterior cingulate cortex	822	23	L&R	4	41	25	-3.56
Dorsal middle cingulate cortex	825	24	R	-6	-4	41	-3.13
Ventral anterior cingulate cortex	1104	24	L&R	0	-30	0	3.26
Insula	1118	13	L	40	-15	0	3.39
Ventral middle cingulate cortex	1235	24	L	4	7	26	3.43
Insula	2014	13	R	-36	-11	-9	3.58
Cerebellar vermis	982		L&R	-7	38	-3	4.02
Ventral frontal cortex	1011	47	L	24	-28	-9	4.46

Table 2: Clusters showing significant group difference of ALFF.

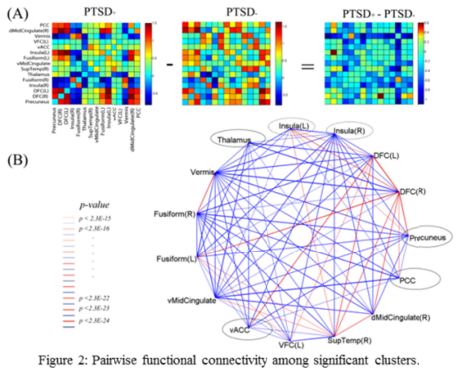

Figure 2: Pairwise functional connectivity among significant clusters.

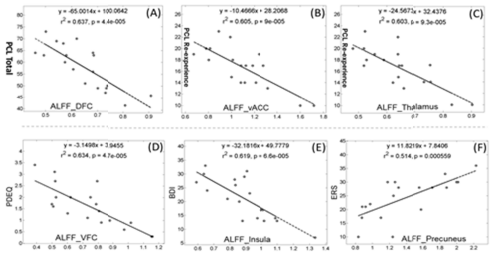

Figure 3: Correlations between regional ALFF scores and clinical scales.

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 1, Table 1), as well as decreased thalamic activity and thalamo-cortical FC[2] (Figure 2). More specifically, decreased spontaneous activity of PTSD+ at dorsal frontal 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 arrhythmia supports a hypothesis brought up by Llinás about thalamic-mediated cognitive binding deficiency for PTSD neuropathology[11].

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