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Reduced default mode network connectivity following combat trauma

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Abstract

Recent studies show decreased functional connectivity in the default mode network (DMN) in PTSD; however, few have directly examined combat trauma specifically. There is limited understanding of how combat itself may affect the DMN. Some literature suggests that trauma exposure, rather than PTSD, can disrupt the DMN. To further elucidate the effect of trauma and PTSD on the DMN, we investigated DMN functional connectivity during the resting-state in veterans with PTSD, combat-exposed controls, and never-traumatized healthy controls. Results revealed that DMN connectivity was reduced in veterans exposed to combat trauma with and without PTSD compared to healthy civilian controls. Specifically, both groups of veterans demonstrated weaker connectivity within a network involving the precuneus, medial prefrontal cortex (mPFC) and right superior parietal lobule regardless of whether the mPFC or precuneus was chosen as a seed region. Findings suggest that the experience of trauma, rather than the pathology of PTSD, may be related to DMN changes.

Keywords

Combat; Trauma; Rest; DMN; PTSD; fMRI

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1. Introduction

Investigations of the neuropathophysiology of posttraumatic stress disorder (PTSD) have become increasingly prevalent. While discrete anatomical entities (e.g., hippocampus, amygdala) have been studied for many years, it is only recently that increasing attention has been paid to network dysregulations that may contribute to the pathogenesis of PTSD. One network drawing particular attention is the default mode network (DMN). The DMN is a brain-based network associated with increases in intrinsic brain activity during resting state and decreases in brain activity during task-related processes [1]. An activation likelihood estimation (ALE) meta-analysis identified main regions of the DMN as the precuneus, posterior and ventral anterior cingulate cortices (PCC; vACC), medial prefrontal cortex (mPFC), bilateral inferior parietal lobules, bilateral middle temporal gyri, and left middle frontal gyrus [2].

Nascent research suggests PTSD is associated with disruptions in the functional connectivity (FC) of the DMN. For example, a study that examined patients with PTSD related to early life trauma exhibited less resting state functional connectivity (rsFC) of the PCC seed region with other areas of the DMN, namely the precuneus, mPFC and bilateral lateral parietal cortex compared to non-traumatized healthy controls; also, the PTSD sample had greater connectivity between the PCC/precuneus seed and right superior frontal gyrus and ventrolateral thalamus [3]. An examination of survivors of motor vehicle accidents found increased rsFC of the PCC with the perigenual ACC and the right amygdala, which was associated with PTSD symptoms [4].

The majority of studies examining DMN integrity and PTSD have been related to civilian trauma; however, less is known about the effect of combat-related trauma on DMN connectivity. PTSD is common following combat exposure during military deployments, particularly those in Iraq and Afghanistan [5]. To date, only two studies have seeded DMN regions to examine combat-related PTSD. Yan et al. observed no difference between veterans with PTSD and combat exposed controls in terms of their precuneal–amygdala FC [6]. However, in the absence of a healthy non-traumatized control group, it is unclear how trauma exposure may be related to altered connectivity. A study by Sripada et al. found that, in comparison to controls (i.e., combat veterans without PTSD and healthy civilians), veterans with PTSD showed increased FC between the PCC seed and the right putamen and right insula [7], and controls showed greater connectivity between the PCC seed and the left hippocampus. However, this paper combined combat exposed veterans and healthy civilians into a single cohort; comparisons between these two groups did not appear to ascertain if the alteration observed in PTSD is also present in combat traumatized veterans without PTSD. This methodological decision raises the question of whether combat exposed individuals and healthy civilians are homogenous enough to be collapsed into a single group.

Although evidence suggests PTSD is associated with DMN disruption, other research raises the question of whether trauma itself, as opposed to the pathology of PTSD, leads to FC alterations. Yan et al. observed that both veterans with PTSD and combat exposed controls had significant positive precuneal–amygdala FC, suggesting a common effect of trauma exposure [6]; additionally, there was no significant difference between groups in terms of

the amount of emotional abuse they experienced in childhood. Relatedly, findings from a non-veteran cohort found participants with early life stress, in the absence of psychiatric illness and medication exposure, demonstrated decreased DMN connectivity [8]. Furthermore, another study that examined DMN activity in adolescent girls found assaultive violence—not PTSD—was associated with heightened connectivity between the parahippocampal gyrus and ventral mPFC and, similarly, the left motor cortex with the precuneus and right parietal cortex [9]. Taken together, these findings may indicate that chronic stress and/or trauma exposure, as opposed to PTSD, leads to disruptions in DMN rsFC.

Given that only two studies have looked at DMN disruptions in PTSD among combat veterans, more research is warranted. Additionally, the precise nature of the DMN's relationship to stress and/or PTSD remains unclear. Thus, the current study investigated DMN FC in veterans with PTSD, combat-exposed controls, and healthy controls. We chose both the precuneus and mPFC as seed regions because these represent key, connected and complementary DMN nodes. The precuneus/PCC is the most commonly used seed region in DMN studies because it shows the highest resting state brain metabolism [10]. Additionally, the precuneus/PCC has demonstrated reliable correlations with other DMN areas in healthy controls e.g., Refs. [11,12]. PTSD has also been associated with alterations in PCC connectivity [3]. In terms of the mPFC, it demonstrates high baseline metabolic activity while the brain is at rest [13]. Furthermore, the mPFC has been observed to correlate with the precuneus during the resting-state [14], and demonstrate dysfunction in PTSD [15]. Therefore, we hypothesized that veterans with PTSD *and* combat-exposed controls (CECs) would show reduced DMN connectivity between key nodes (mPFC and precuneus) compared to healthy civilians. Additionally, we posited that there would be further reductions in connectivity between DMN nodes in veterans with PTSD compared to CECs.

2. Methods

2.1. Participants

Male veterans were recruited from the Veteran Affairs Ann Arbor Healthcare Systems as well as through community advertisements. The veterans ($n = 40$), who had served in Operation Enduring Freedom/Operation Iraqi Freedom, were classified either as CEC or patients with PTSD. Although females were not explicitly excluded, no female veteran participants meeting eligibility criteria were enrolled. For comparison, healthy civilian males (HC) who had no history of trauma were recruited through community advertisements. A subset of our participants had previously been examined for differences in rsFC using an amygdala seed [16].

Psychiatric diagnoses were established via the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV (SCID-IV) [17]. Additional assessment measures included the Clinician Administered PTSD Scale (CAPS) [18], PTSD Checklist, military version (PCL-M) [19], Combat Exposure Scale (CES) [20], the Hamilton Depression Rating Scale (Ham-D) [21], and the Beck Depression Inventory (BDI-II) [22]. The SCID was used as the primary instrument to diagnose PTSD and other Axis I disorders. In addition, we used the CAPS to measure PTSD severity and included subjects with a

CAPS score of at least 40; while low as a diagnostic cut-off criteria on its own does reflect moderate PTSD severity and we aimed to study a wide range of PTSD severity to investigate individual differences in between PTSD symptom severity and functional connectivity strength. Of note, all subjects in the PTSD group ($n = 22$) had a CAPS score 50. Veterans were included in the CEC group with a CAPS score <20 , and with no prior lifetime DSM-IV diagnosis of PTSD; CEC subjects were also excluded if they had any Axis I diagnosis. Similarly, HCs were assessed to ensure they had no history of Axis I disorders. All subjects were negative on urine screen, had no history of neurological illness or major medical problems, and were free of psychoactive medications at the time of scanning. All subjects including those PTSD group free of psychotropic medications for at least 4 weeks; in fact, only 7 of the PTSD subjects had lifetime history of psychotropic use and all were >3 months free of psychotropic medication use. All were compensated for their time and provided written informed consent and the protocol was approved by the VA Ann Arbor Healthcare System Human Subjects Committee and University of Michigan Institutional Review Board.

2.2. Functional imaging acquisition

Blood oxygen level-dependent (BOLD) sensitive whole-brain fMRI scanning was performed on a 3.0 T GE Signal System (General Electric; Milwaukee, WI) using a four-channel GE Quadrature sending and receiving head coil using a T2*-sensitive gradient echo reserve spiral acquisition sequence optimized to minimize susceptibility to artifact (signal loss) at the medial temporal lobe [23]. All veterans and eight healthy control functional images were acquired from a sequence with the following parameters: 43 axial, 3-mm-thick slices; 2 s repetition time; 30 ms echo time; 64×64 matrix; 220 mm field of view; flip angle 90° . The remaining five healthy control functional images were acquired with a sequence with the following parameters: 30 axial, 5-mm-thick slices; 2 s repetition time; 25 ms echo time; 64×64 matrix; 240 mm field of view; flip angle 77° . Subsequent analysis revealed that removing the 5HCs scanned using different parameters did not alter the reported findings below. Additionally, a high-resolution, T1-weighted volumetric anatomical scan (three-dimensional spoiled gradient echo) was acquired in the same plane for anatomical localization and spatial normalization. All subjects participated in an 8-min scan and were instructed to focus on a white fixation cross.

2.3. Functional imaging analysis

Individual functional images were analyzed using CONN: functional connectivity toolbox [24] with preprocessing steps integrated from Statistical Parametric Mapping software (SPM8; <http://www.fil.ion.ucl.ac.uk/spm/>). Images underwent motion correction, slice-time correction, and were normalized to the Montreal Neurological Institute (MNI) template, and smoothed with an 8 mm^3 Gaussian kernel to minimize effects of individual functional and anatomical differences. Participants moving more than 3 mm in any direction were excluded. Importantly the groups did not differ in measures of total or maximum indices of head motion per SPM realignment parameters (Total [Mean $\pm$ SD] in mm: HC = 1.00 ± 0.81 ; CEC = 1.11 ± 0.71 ; PTSD = 1.2 ± 0.68 ; Max: HC = 0.45 ± 0.36 ; CEC = 0.47 ± 0.37 ; PTSD = 0.60 ± 0.43 ; all $p_s > 0.45$). Moreover, the 6 motion parameters for each subject were entered into 2nd level group analyses were entered as covariates of no interest. As pre-

determined seed regions within CONN toolbox, the precuneus (MNI coordinates: [0, -56, 28]) and mPFC (MNI coordinates: [0, 54, -8]) have shown reliable patterns of DMN FC through voxel analysis [24]. These areas were used as seed regions of interest in seed-to-voxel whole brain analyses. The entire BOLD time course was extracted from mPFC and precuneus seeds, and Pearson's correlation coefficients were calculated between these entire time courses and the time courses of all other voxels across the brain and a mean time course across the entire region of interest. To illustrate direction of group differences, connectivity values (arbitrary units [a.u.]) were then extracted from a 10 mm sphere centered on each ROI peak using SPM8. Fisher transformation was used to convert the resulting correlation coefficient into Z scores which were then used in second-level general linear model analyses. PTSD, CECs, and HCs were compared using two analyses of variance (ANOVA), one for each seed. Subsequent simple effects analyses were conducted of extracted connectivity strength to identify direction of effects. Simple effects analyses and Pearson's correlations were conducted in SPSS (Version 20; Chicago, IL). Whole-brain maps were examined at an *uncorrected* voxel threshold of $p < 0.001$ with minimum cluster size of 20 voxels to determine significant main effect of group, to balance between Type I and Type II error and achieves false discovery rate of 0.05 as noted by Lieberman and Cunningham [25], and to make comparisons to prior studies of DMN rsFC in PTSD [7].

3. Results

3.1. Demographics

Demographic and clinical variables are summarized in Table 1.

3.2. Medial prefrontal cortex seed

A main effect of group was observed in rsFC between the mPFC seed and pC and right superior parietal lobule (Fig. 1A and B ; Table 2). Follow up independent samples *t*-tests revealed that relative to HCs (Mean [*M*] ± Standard Deviation [SD] rsFC values [a.u.]; *M*: 0.73 SD: ± 0.17), both the PTSD (*M*: 0.41 SD: ± 0.13; $t(33) = -6.15$, $p < 0.001$) and CEC (*M*: 0.42 SD: ± 0.15; $t(29) = 5.37$, $p < 0.001$) groups exhibited less rsFC between mPFC and pC; no significant difference was observed between PTSD and CEC groups ($t(38) = 0.11$, $p = 0.91$). HCs (*M*: 0.17 SD: ± 0.09) also had greater rsFC between the mPFC and right superior parietal lobule (SPL) when compared to PTSD (*M*: 0.02 SD: ± 0.14; $t(33) = 3.64$, $p = 0.001$) and CEC (*M*: -0.05 ± SD: 0.14; $t(29) = 5.04$, $p < 0.001$) groups; no significant difference was observed between PTSD and CEC groups ($t(38) = 1.46$, $p = 0.154$).

3.3. Precuneus seed

A main effect of group was observed in rsFC between the precuneus seed and the mPFC and right SPL (Fig. 2A and B ; Table 2). Follow up independent samples *t*-tests revealed that relative to HCs (*M*: 1.44 SD: ± 0.24), both PTSD (*M*: 1.17 SD: ± 0.19; $t(33) = -3.67$, $p = 0.001$) and CEC (*M*: 1.23 SD ± 0.23, $t(29) = -2.43$ $p = 0.021$) groups exhibited less rsFC between the precuneus and mPFC; there was no significant difference between PTSD and CEC groups ($t(38) = 0.959$, $p = 0.34$). In addition, HCs (*M*: 0.11 SD: ± 0.6) exhibited stronger functional coupling between the precuneus and SPL when compared to PTSD (*M*: 0.002 SD: ± 0.09; $t(33) = 3.87$, $p < 0.001$) and CEC (*M*: -0.01 SD: ± 0.11; $t(29) = 3.46$, $p =$

0.002) groups; there was no significant difference between PTSD and CEC groups ($t(38) = 0.372, p = 0.71$).

3.4. Correlations between connectivity values and symptom measures

Pearson's correlation coefficient analyses between rsFC values and clinical scores for depression, anxiety, PTSD and combat exposure in the veteran groups were non-significant.

4. Discussion

Using rsfMRI, we examined DMN connectivity in OEF/OIF veterans with PTSD, CECs and HCs never previously traumatized. Our central finding was reduced DMN connectivity among all veterans as compared to healthy civilian controls. Specifically, both groups of veterans separately demonstrated less resting-state mPFC connectivity to the precuneus and right superior parietal lobule (SPL). Similarly, the veteran groups also demonstrated less resting-state precuneus connectivity to the mPFC and to the right SPL. There was a remarkable convergence of findings from *both* the precuneus and mPFC seeds, suggesting a common focal network disruption confined to the DMN following combat trauma.

While several studies have reported DMN abnormalities in people with PTSD, e.g., Refs. [3,4], our results suggest that the combat trauma, as opposed to the diagnosis of PTSD alone, is associated with resting state disruptions. To date, only two other studies have seeded the DMN in combat veterans with PTSD [6,7]. Sripada et al. found that veterans with PTSD showed increased FC between the PCC seed and the right putamen as well as the right insula [7]. Yan et al. found PTSD to be associated with less precuneus–mPFC connectivity, but found no group differences in precuneal–amygdala functional connectivity [6]. Notably, both of these veteran-focused studies found connectivity between the DMN and extra-DMN networks, while our findings indicate reduced connectivity within nodes (precuneus, mPFC and superior parietal cortex) of the DMN alone.

Earlier work by Greicius et al. used both fMRI and DTI to establish that rsFC between the mPFC and PCC also reflected structural connectivity in their study of healthy adults [26]. In the present study, healthy individuals showed greater functional connectivity than their traumatized counterparts. Thus, it is possible our findings may be related to an underlying impaired structural connection between the mPFC and PCC for trauma survivors. Future work that investigates structural connectivity in trauma-exposed individuals would further our understanding of how trauma affects the DMN.

Yan et al. found no distinction between precuneal–amygdala connectivity in a PTSD cohort of veterans and CECs, which suggests a potential lack of distinction between PTSD patients and CECs in certain aspects of DMN functioning [7]. Supporting our findings further are studies that suggest stress exposure, and not psychiatric illness, may disrupt the DMN. For example, Philip et al. found that early life stress, in the absence of psychiatric illness and medication, was related to decreased connectivity between the PCC seed and mPFC [8]. Another study indicated that, in healthy adults, childhood poverty reduced PCC to vmPFC connectivity as compared to adults raised in middle-income households [27]. Further investigation of chronic stress, including early life stress, on the DMN will do much to

enrich our understanding of changes to large-scale intrinsic connectivity networks. Interestingly, although there are some studies that suggests stress decreases connectivity in the DMN, an animal study [28] and a study of medical students [29] found that exposure to prolonged stress was related to increased DMN activity. Of note, Kennis et al. [30] recently showed reduced resting state connectivity between the perigenual ACC (as part of the mPFC and DMN) and the superior medial frontal gyrus and medial temporal gyrus in traumatized subjects *with and without* PTSD, relative to controls, consistent with our findings. Therefore, understanding how chronic stress can affect the DMN will do much to inform understanding of the relationships between trauma exposure, PTSD, and/or alterations in brain structure-function. It is noteworthy that we did not observe a correlation between rsFC values and combat exposure across veterans. This could may be due to an insufficient sample size to test this relationship directly. Moreover, trauma exposure may be only one factor that contributes to the strength of DMN resting state connectivity. Alternatively, other factors that may be common to all veterans exposed to trauma (e.g., pre- and post-deployment stressors, military experience) may explain or contribute to reduced DMN rsFC.

This study has several limitations. First, these analyses, embedded in a cross-sectional design, are correlational and do not permit causal inferences. Additionally, since only male veterans with combat exposure were included in the study, the generalizability of our findings is limited to combat trauma in men. Given the lack of correlation between combat exposure and PTSD symptom severity in our data, the functional and clinical relevance of less DMN connectivity between traumatized and non-traumatized groups remains unclear. Future studies examining how extent and type of trauma is related to DMN rsFC may elucidate the relationship between trauma and brain network function. Although a post hoc analysis removing the 5HCs scanned using different parameters did not alter the reported findings below, differences in acquisition parameters may have confounded the results. Lastly, given the small sample size, results should be considered preliminary. Of note, data collection for study was completed in 2012 and thus DSM-IV criteria was used to diagnose PTSD. Now that the PTSD diagnostic criteria has been modified in DSM-5, it will be important to examine whether trauma exposure and/or differences PTSD criteria (between DSMIV and DSM-V) impact brain function findings including DMN rsFC. Mamar and colleagues have recently demonstrated differences in measuring and detecting PTSD using DSM-IV-TR versus DSM-5 can affect the inclusion of participants in the “PTSD group” with fewer participants meeting the more stringent DSM-5 criteria [31].

In conclusion, this study found reduced rsFC within the DMN among veterans exposed to combat trauma as compared to healthy civilians, who were non-traumatized controls, and that DMN connectivity did not differentiate veterans with and without PTSD exposed to similar levels of combat trauma. These findings suggest that disruption of DMN connectivity at rest reflects combat stress exposure, as opposed to illness per se. They also prompt future study of the relevance of functional network dysfunction as a consequence of stress and trauma.

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HIGHLIGHTS

- PTSD has been associated with disruptions of the default mode network (DMN).
- Most DMN–PTSD studies focus on civilian trauma. Less is known about combat-related trauma.
- We examined DMN in veterans with PTSD, veterans without PTSD, and healthy civilians.
- Results indicate DMN connectivity did not differentiate veterans with and without PTSD.
- Findings suggest DMN disruption reflects combat exposure, as opposed to illness per se.

Fig. 1. Main effect of group on resting state functional connectivity (rsFC) using medial prefrontal cortex (mPFC) seed localized to A precuneus and B right superior parietal lobule (SPL). Post hoc *t*-tests of extracted rsFC values (β weights, arbitrary units [a.u.]) from precuneus and SPL reveal significant differences between HCs and both groups of veterans (HC > CEC, HC > PTSD) but not between PTSD and CEC groups. Threshold for displaying the image is set at $p < 0.001$, uncorrected.

Fig. 2. Main effect of group on resting state functional connectivity (rsFC) using precuneus seed localized to A medial prefrontal cortex (mPFC) and B right superior parietal lobule (SPL). Post hoc *t*-tests of extracted rsFC values (β weights, arbitrary units [a.u.]) from mPFC and SPL reveal significant differences between HCs and both groups of veterans (HC > PTSD, HC > CEC) but not between PTSD and CEC groups. Threshold for displaying the image is set at $p < 0.001$, uncorrected.

Table 1

Group demographic and clinical characteristics.

	Group mean ($\pm$ SD)		CEC and PTSD <i>t</i> -test		CEC-HC <i>t</i> -test	PTSD-HC <i>t</i> -test
	PTSD	CEC	HC			
<i>n</i> = 53	22	18	13			
Age	29.8 $\pm$ 7.6	33.9 $\pm$ 9.2	25.4 $\pm$ 7.6	n.s.	CEC > HC*	n.s.
CAPS	68.6 $\pm$ 12.6	5.6 $\pm$ 5.7	N/A	PTSD > CEC**		
PCL-M	54.2 $\pm$ 8.0	26.8 $\pm$ 11.4	N/A	PTSD > CEC**		
BDI-II	22.0 $\pm$ 6.6	6.1 $\pm$ 6.8	N/A	PTSD > CEC**		
HAM-D	10.6 $\pm$ 3.7	2.3 $\pm$ 2.5	N/A	PTSD > CEC**		
CES	24.7 $\pm$ 6.5	21.2 $\pm$ 5.5	N/A	n.s.		

PTSD, posttraumatic stress disorder; CEC, combat-exposed controls; HC, healthy controls.

Clinician Administered PTSD Scale (CAPS); PTSD Checklist, military version (PCL-M); Beck Depression Inventory (BDI-II); Hamilton Depression Rating Scale (HAM-D); Combat Exposure Scale (CES).

n.s., non-significant ($p > 0.05$).* $p < 0.001$.** $p < 0.001$.

Table 2

Resting state functional connectivity: main effect of group.

Regions	X	Y	Z	Cluster size (voxels)	Z score
Precuneus seed					
Medial prefrontal cortex	2	60	-6	133	4.64
Right superior parietal lobule	24	-66	68	67	3.98
Medial prefrontal cortex seed					
Precuneus	2	-67	26	206	5.49
Right superior parietal lobule	24	-70	62	70	3.72

Significant clusters at an uncorrected voxel threshold of $p < 0.001$ with minimum cluster size of 20 voxels.