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Default Mode Network Subsystems Are Differentially Disrupted in Posttraumatic Stress Disorder

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ABSTRACT

BACKGROUND: Posttraumatic stress disorder (PTSD) is a psychiatric disorder characterized by debilitating re-experiencing, avoidance, and hyperarousal symptoms following trauma exposure. Recent evidence suggests that individuals with PTSD show disrupted functional connectivity in the default mode network, an intrinsic network that consists of a midline core, a medial temporal lobe (MTL) subsystem, and a dorsomedial prefrontal cortex (PFC) subsystem. The present study examined whether functional connectivity in these subsystems is differentially disrupted in PTSD.

METHODS: Sixty-nine returning war veterans with PTSD and 44 trauma-exposed veterans without PTSD underwent resting-state functional magnetic resonance imaging. To examine functional connectivity, seeds were placed in the core hubs of the default mode network, namely the posterior cingulate cortex (PCC) and anterior medial PFC, and in each subsystem.

RESULTS: Compared to control subjects, individuals with PTSD had reduced functional connectivity between the PCC and the hippocampus, a region of the MTL subsystem. Groups did not differ in connectivity between the PCC and dorsomedial PFC subsystem or between the anterior medial PFC and any region within either subsystem. In the PTSD group, connectivity between the PCC and hippocampus was negatively associated with avoidance/numbing symptoms. Examination of the MTL and dorsomedial PFC subsystems revealed reduced anticorrelation between the ventromedial PFC seed of the MTL subsystem and the dorsal anterior cingulate cortex in the PTSD group.

CONCLUSIONS: Our results suggest that selective alterations in functional connectivity in the MTL subsystem of the default mode network in PTSD may be an important factor in PTSD pathology and symptomatology.

Keywords: Avoidance, Default mode network, Functional connectivity, Medial temporal lobe, PTSD, Resting state fMRI

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Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder that develops after exposure to highly distressing and life-threatening events. The most common features of PTSD include re-experiencing of the trauma (e.g., flashbacks), avoidance (e.g., avoiding trauma-related stimuli or trauma-evoking situations), and hyperarousal symptoms (e.g., hypervigilance). Current neurocircuitry models of PTSD suggest that the medial prefrontal cortex and hippocampus are critically involved in mediating the disorder (1–7). According to these models, abnormal structure and function of the ventromedial prefrontal cortex (vMPFC) in PTSD results in a failure to regulate activity in brain regions that are important for fear expression and appraisal, leading to an exaggerated fear response (3,4,8–13). In addition, alterations in hippocampal function in PTSD may contribute to impaired contextual fear learning (3,4,9,10) and impaired contextual fear extinction recall (11,14,15), an adaptive process that relies on both the hippocampus and vMPFC (16–19). Taken together, these studies suggest that PTSD is associated with dysregulation of a frontal–medial temporal lobe (MTL) circuit that results in an exaggerated fear response and an inability to extinguish this fear when the context no longer predicts threat.

More recently, studies have used resting-state functional magnetic resonance imaging (fMRI) to examine connectivity among brain regions that form integrated networks in PTSD. One such network is the default mode network (DMN), which includes the MTL, posterior cingulate cortex (PCC), medial PFC, inferior parietal lobule, and lateral temporal cortex (20). Several studies have found PTSD-related alterations in the DMN (21–26), and a recent meta-analysis found that PTSD is consistently associated with reduced functional connectivity (27). Evidence in healthy individuals suggests that the DMN can be further fractionated into a midline core consisting of the PCC and anterior medial PFC (aMPFC) and two functionally and anatomically distinct subsystems (28): an MTL system that includes the vMPFC, posterior inferior parietal lobule,

retrosplenial cortex, parahippocampal cortex, and hippocampal formation, and a dorsomedial PFC (dMPFC) system that includes the dMPFC, temporoparietal junction, lateral temporal cortex, and temporal pole. These subsystems are differentially affected by MTL lesions (29) and are thought to be involved in distinct cognitive processes (28,30). For example, the MTL subsystem includes regions that are important for learning and memory (30), while the dMPFC subsystem includes regions that are critical for mentalizing and social processing of the self and others (30–32). Although there is evidence that connectivity within the DMN is compromised in PTSD (21–25,27,33), it is currently unknown whether the subsystems of the DMN are differentially disrupted. Because memory alterations appear to be a core feature of the disorder (34,35), we predicted that the MTL subsystem might be particularly affected in PTSD.

In addition to disruptions to the DMN, other networks are also altered in PTSD (23,25,27,36). Networks such as the salience network and central executive network are engaged during externally directed and attention-demanding tasks and are anticorrelated with the DMN. Daniels *et al.* (36) found that individuals with PTSD may have difficulty disengaging the DMN and engaging salience and central executive networks during attention-demanding tasks. In addition, there appears to be increased cross-network connectivity between the DMN and salience network in PTSD at rest (23,27), which suggests that neural networks may be less differentiated in PTSD.

To date, no studies have examined whether there is differential involvement of the DMN subsystems. It is also unknown how these subsystems interact with the salience and central executive networks in PTSD. Although one study (23) examined the connectivity between the DMN and salience network in PTSD using an anterior and posterior DMN seed, these seeds were not selected to probe the distinct subsystems. Here, we used seed-based resting-state fMRI in a large cohort of trauma-exposed war veterans to examine how PTSD affects these DMN subsystems. Given the critical role of the vMPFC and hippocampus in PTSD—two areas associated with the MTL subsystem of the DMN—we hypothesized that PTSD would be associated with decreased DMN functional connectivity specific to the MTL subsystem. In addition, considering recent evidence for diminished network segregation in PTSD (23,27), we hypothesized that PTSD would be associated with increased connectivity (i.e., reduced anticorrelation) between the DMN and regions outside of the DMN, such as those in the salience and central executive networks.

METHODS AND MATERIALS

Participants

One hundred thirty-four individuals who were deployed overseas between 1999 and 2013 were recruited for this study through the Veterans Affairs Boston Polytrauma Network and through community outreach as part of a larger study on the cognitive and neural sequelae of mild traumatic brain injury (mTBI) and PTSD. Exclusionary criteria for the larger study were age >50 years and questionable effort as determined by raw scores <45 on the retention trial of the Test of Memory Malingering (37). Seven participants were excluded from the study because they had a history of predeployment TBI with loss of consciousness or with symptoms persisting >3 months postinjury ($n = 4$) or MRI contraindications ($n = 3$). An additional 14 participants were excluded after scanning because structural brain abnormalities (e.g., hemorrhages or hematomas) were seen on T2–fluid-attenuated inversion recovery scans, susceptibility-weighted imaging, or T1-weighted sequences as determined by a board-certified neuroradiologist ($n = 5$), MRI scan malfunction ($n = 4$), or because it was subsequently discovered that they did not meet entry criteria for the study (one participant was not a veteran, one had no history of trauma exposure, and three were suspected of having an alcohol-related disorder).

Of the 113 U.S. veterans included in the final sample (see Table 1 for participant characteristics and Supplemental Table S1 for medication details), 69 met the DSM-IV criteria for current PTSD as assessed via the Clinician-Administered PTSD Scale (CAPS) (38). The remaining 44 participants

Table 1. Demographic and Clinical Characteristics

Variable	Controls ($n = 44$)	PTSD ($n = 69$)	Group Comparison
Age in Years, Mean (SD)	29.2 (6.1)	29.4 (6.4)	Mann-Whitney $U = 1498.5$, $p = .9$
Males, *n* (%)	40 (90.9)	67 (97.1)	$\chi^2_1 = 2.1$, $p > .1$
WTAR *Z* Score, Mean (SD)	0.4 (0.9)	0.4 (0.7)	Mann-Whitney $U = 1434.5$, $p = .6$
Current Alcoholic Drinks Per Week, Mean (SD)	4.5 (5.9)	5.8 (8.9)	Mann-Whitney $U = 1398.5$, $p = .5$
CAPS Total, Mean (SD)	25.0 (14.1)	70.4 (18.1)	$t_{111} = -14.1$, $p < .001$
CAPS Re-experiencing, Mean (SD)	6.8 (5.8)	18.5 (7.8)	$t_{109} = -8.5$, $p < .001$
CAPS Avoidance/Numbing, Mean (SD)	7.4 (6.8)	27.0 (9.2)	$t_{107.3} = -12.9$, $p < .001$
CAPS Hyperarousal, Mean (SD)	10.8 (7.0)	24.2 (6.6)	$t_{109} = -10.2$, $p < .001$
mTBI Diagnosis, *n* (%)	14 (31.8)	45 (65.2)	$\chi^2_1 = 12.0$, $p = .001$
Combat Exposure, Mean (SD)	7.6 (4.3)	10.6 (3.1)	$t_{72.1} = -4.0$, $p < .001$
Beck Depression Inventory II, Mean (SD)	10.0 (8.3)	22.0 (10.2)	$t_{111} = -6.6$, $p < .001$
Medication, *n* (%)	9 (20.5)	35 (50.7)	$\chi^2_1 = 10.4$, $p = .001$
Childhood Trauma Exposure, *n* (%)	5 (11.4)	9 (13.0)	$\chi^2_1 = 0.08$, $p = .8$

For ease of interpretation, we report the means and SDs for variables that were not normally distributed. Information on whether an individual was exposed to childhood trauma was collected as part of the CAPS interview.

CAPS, Clinician-Administered PTSD Scale; mTBI, mild traumatic brain injury; PTSD, posttraumatic stress disorder; WTAR, Wechsler Test of Adult Reading.

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