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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 (dMPFC) 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 MRI (rs-fMRI). 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 (aMPFC), and in each subsystem.

Results—Compared to controls, 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 dMPFC subsystem or between the aMPFC 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 dMPFC subsystems revealed reduced anticorrelation between the ventromedial PFC (vMPFC) seed of the MTL subsystem and the dorsal anterior cingulate cortex in the PTSD group.

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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

PTSD; resting state fMRI; default mode network; medial temporal lobe; functional connectivity; avoidance

Introduction

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 important for fear expression and appraisal, leading to an exaggerated fear response (3, 4, 8–13). Further, 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 MRI (rs-fMRI) to examine connectivity among brain regions that form integrated networks in PTSD. One such network is the default mode network, which includes the MTL, posterior cingulate cortex (PCC), medial prefrontal cortex, inferior parietal lobule, and lateral temporal cortex (20). Several studies have found PTSD-related alterations in the default mode network (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 default mode network can be further fractionated into a midline core consisting of the PCC and anterior medial prefrontal cortex (aMPFC) and two functionally and anatomically distinct subsystems (28): a MTL system that includes the vMPFC, posterior inferior parietal lobule, retrosplenial cortex, parahippocampal cortex, and hippocampal formation; and a dorsomedial prefrontal cortex (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 default mode network is compromised in PTSD (21–25, 27, 33), it is currently unknown whether the subsystems of the default mode network are differentially disrupted. As 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 default mode network, 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 default mode network. Daniels et al. (36) found that individuals with PTSD may have difficulty disengaging the default mode network and engaging salience and central executive networks during attention-demanding tasks. Further, there appears to be increased cross-network connectivity between the default mode network 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 default mode network subsystems. Additionally, it is unknown how these subsystems interact with the salience and central executive networks in PTSD. Although one study (23) examined the connectivity between the default mode and salience networks in PTSD using an anterior and posterior default mode network seed, these seeds were not selected to probe the distinct subsystems. Here, we used seed based rs-fMRI in a large cohort of trauma-exposed war Veterans to examine how PTSD affects these default mode network subsystems. Given the critical role of the vmPFC and hippocampus in PTSD, two areas associated with the MTL subsystem of the default mode network, we hypothesized that PTSD would be associated with decreased default mode network functional connectivity specific to the MTL subsystem. Additionally, in light of 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 default mode network and regions outside of the default mode network, such as those in the salience and central executive networks.

Materials and Methods

Participants

One hundred thirty four individuals, deployed overseas between 1999 and 2013, were recruited for this study through the VA Boston Polytrauma Network and through community outreach as part of a larger study on the cognitive and neural sequelae of mTBI and PTSD. Exclusionary criteria for the larger study were age > 50 years and questionable effort as determined by raw scores below 45 on the retention trial of the Test of Memory Malingering (TOMM; 37). Seven participants were excluded from the study because they had a history of pre-deployment traumatic brain injury (TBI) with loss of consciousness (LOC) or with symptoms persisting longer than three months post injury (n=4), or magnetic resonance imaging (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-FLAIR, susceptibility weighted imaging (SWI), 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 DSM-IV criteria for current PTSD as assessed via the Clinician-Administered PTSD scale (CAPS; 38). The remaining 44 participants experienced a criterion A trauma event, but did not meet criteria for PTSD. For two participants, the CAPS was not available; therefore, current PTSD status was determined using a cut-off score of 50 on the PTSD Checklist-Military Version (PCL-M; 39).

All individuals underwent an extensive clinical TBI interview with a neuropsychologist, which is described in detail in Verfaellie, Lafleche, Spiro, Tun, and Bousquet (40). Participants were classified as having no-TBI, mild TBI without LOC, or mild TBI with LOC. mTBI status was used as a covariate in all analyses.

Image Acquisition

Scans were collected with a 12-channel head coil on a 3-Tesla Siemens Trio whole-body MRI scanner located at the VA Boston Healthcare System, Jamaica Plain campus. Two high-resolution structural T1-weighted magnetization-prepared rapid gradient-echo (MP RAGE) sequences were collected for each participant: parameters for the first 28 participants¹ included FOV=256, Matrix=240 × 256, 160 slices, 1 × 1 × 1.2 mm voxels, TR=2300 ms, TE=2.98 ms, flip angle=9°; parameters for the remaining participants included FOV=256, Matrix=256 × 256, 176 slices, 1 × 1 × 1 mm voxels, TR=2530 ms, TE=3.32 ms, flip angle=7°. Two six-minute whole-brain functional image series were acquired parallel to the anterior commissure-posterior commissure plane using an echoplanar imaging sequence sensitive to the blood oxygenation level dependent (BOLD) signal: slice order = interleaved, matrix = 64², FOV = 192, thickness = 3.75 mm, voxel size = 3 × 3 × 3.75 mm, volumes = 120, TR = 3000 msec, TE = 30 msec, flip angle = 90°. The first five volumes were discarded from each run to allow for equilibration of the scanner signal. Participants were instructed to remain still with their eyes open during fMRI data collection.

Image Processing and Analysis

All preprocessing steps and analyses were carried out using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) FSL software package (version 4.1.5; <http://www.fmrib.ox.ac.uk/fsl>). FMRI data were processed using FSL's fMRI Expert Analysis Tool (FEAT; Version 5.98). The following pre-statistics processing was applied: motion correction using MCFLIRT (41), slice-timing correction using Fourier-space time-series phase-shifting, non-brain removal using BET (42), spatial smoothing using a Gaussian kernel of fixed-width half-maximum (FWHM) 6.0mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting with $\sigma=45.0$ s), and Gaussian low-pass temporal filtering half-width half-maximum (HWHM) 2.8s. Registration to high-resolution structural and standard space images was carried out using FMRIB Linear Registration Tool (FLIRT; 41, 43). Registration from high-resolution structural to standard

¹Because differences in the structural MP RAGE sequence could potentially impact registration, we examined functional connectivity as a function of the MP RAGE acquisition parameters. Results revealed no significant differences in functional connectivity.

space was further refined using FMRIB Nonlinear Image Registration Tool (FNIRT; 44, 45). Two T1-weighted volumetric images were averaged and then reconstructed using the FreeSurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>) version 5.0 for each participant. This averaged, high resolution image was then used for within subject registration of structural and functional images.

Whole-brain rs-fMRI analyses were performed using a seed-based approach. Seeds consisted of four 8 mm spherical ROIs obtained from Andrews-Hanna et al. (28): PCC (MNI coordinates = -8, -56, 26), aMPFC (MNI coordinates = -6, 52, -2), dMPFC (MNI coordinates = 0, 52, 26), and vMPFC (MNI coordinates = 0, 26, -18). The PCC and aMPFC seeds were chosen because they represent the two core hubs of the default mode network; the dMPFC and vMPFC seeds were selected because they represent the core hubs of the dMPFC and MTL subsystems, respectively. Regions of interest (ROI) for cerebrospinal fluid, white matter, and whole brain were created using FreeSurfer. All seeds and ROIs were first transformed to each individual's native space and then the mean time series (based on all of the voxels within the region) was computed. Next, we completed a whole-brain voxel-wise analysis assessing the correlation between the seed region and the rest of the brain, with nuisance regressors (cerebrospinal fluid, white matter, and whole brain time-series along with the six motion parameters) included in the model. To ensure that the regression of the global signal did not create spurious anticorrelations in the data (46), we re-analyzed the data without regressing out the whole brain time-series. The pattern of results did not change and is therefore not reported. Head motion parameters were also examined across groups. Groups did not significantly differ in absolute or relative head motion.

To examine connectivity with each of the four seeds, BOLD runs were combined for each participant² using a fixed effects model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects; 47, 48, 49). To determine connectivity differences across groups, group level connectivity maps were generated for each seed using mixed effects model FLAME stage 1 (47, 48, 49). Age, current alcohol use (number of drinks per week), and mTBI group status were entered into the model as regressors. Z statistic images were thresholded using clusters determined by $Z < 2.3$ with a corrected cluster significance threshold of $P = 0.05$.

Although false positives are less of a concern with resting state data when using FLAME, given the recent discussion of cluster-wise thresholds (50), we re-examined our data using the spatial autocorrelation function (ACF) and Monte Carlo α simulation in the Analysis of Functional NeuroImages (AFNI version 16.2.09; <http://afni.nimh.nih.gov/afni>; 51) program. Details of this analysis are reported in the Supplemental Materials. The results were consistent with our previous approach, with final results reported using FSL's FLAME program.

To examine associations between functional connectivity and PTSD symptom cluster scores, Z -values of significant functional connectivity clusters in the group contrast were extracted from connectivity maps and entered into SPSS, version 19 (IBM Corp., Armonk, NY).

²Five participants had only one BOLD run available for analysis.

Pearson correlations were calculated between these Z -values and CAPS re-experiencing, avoidance/numbing, and hyperarousal scores. Two participants, for whom CAPS scores were not available, were excluded from these analyses. Bonferroni correction was used to correct for multiple comparisons.

Results

Functional Connectivity of the Default Mode Network Hubs and Subsystems

Inspection of the two midline core hubs revealed that the PCC and aMPFC seeds showed positive connectivity with regions typical of the default mode network for both groups, including medial frontal cortex, middle temporal gyrus, and precuneus/PCC (Figure 1, Supplemental Table S2). Both seeds showed anticorrelations with regions associated with task-positive networks (salience network and central executive network; Figure 1), including the insula, frontal gyri, and parietal lobe (Supplemental Table S2). DMPFC and vMPFC seeds, representing the two subsystems, showed positive connectivity with regions of the default mode network and anticorrelations with regions of the salience and central executive networks for both groups (Figure 1, Supplemental Table S2).

Functional Connectivity in PTSD Versus Controls

Connectivity of the default mode network core hubs—Using the PCC as a seed, individuals with PTSD in comparison to controls showed reduced functional connectivity with the hippocampus, a region of the MTL subsystem (Figure 1, Table 2). Groups did not differ in functional connectivity between the PCC and regions of the dMPFC subsystem. No group differences were observed in connectivity between the aMPFC seed and any region.

Connectivity of the default mode network subsystems—Examination of seeds from each default mode network subsystem revealed that individuals with PTSD had significantly reduced anticorrelation between the vMPFC seed of the MTL subsystem and the dorsal anterior cingulate cortex (Figure 1, Table 2). In contrast, there were no significant group differences in connectivity between the dMPFC seed of the dMPFC subsystem and any region.

Effects of mTBI and other covariates—Although the initial analyses controlled for mTBI status, we also examined whether mTBI affected PCC-hippocampal or vMPFC-dorsal anterior cingulate cortex connectivity, which our main analysis showed to be altered by PTSD. The effect of mTBI was not significant (all P s > 0.2). We also probed in additional models whether medication status, combat exposure, or childhood trauma contributed to the observed effects of PTSD. These additional covariates did not reveal any significant associations with PCC-hippocampal or vMPFC-dorsal anterior cingulate cortex functional connectivity either (all P s > 0.1). PTSD remained a significant predictor in the functional connectivity of these regions after inclusion of these covariates in the models (all P s < 0.001).

Effects of depression—Depression and PTSD were highly correlated in our sample ($r = 0.70$, $P < 0.001$), raising the question as to whether the observed PTSD alterations could be

linked specifically to PTSD. To examine this question, depression symptom severity (as measured by the Beck Depression Inventory-II) was included as an additional predictor in hierarchical linear regression models. The pattern of results did not change.

Correlations Between Functional Connectivity and PTSD Symptom Cluster Scores

Within the PTSD group, PCC-hippocampal connectivity was negatively associated with avoidance/numbing symptoms ($r = -0.37$, $P = 0.002$, Figure 2A); that is, reduced PCC-hippocampal connectivity was associated with greater avoidance/numbing symptoms. This association was not significant for controls ($r = -0.09$, $P = 0.58$, Figure 2B). There were no significant associations between PCC-hippocampal connectivity and re-experiencing (PTSD: $r = -0.16$, $P = 0.21$; Controls: $r = 0.01$, $P = 0.94$) or hyperarousal (PTSD: $r = -0.18$, $P = 0.15$; Controls: $r = 0.18$, $P = 0.24$) symptoms. The functional connectivity between the vMPFC and dorsal anterior cingulate cortex was not significantly associated with any PTSD symptom cluster score.

Discussion

To our knowledge, this is the first study to examine resting-state functional connectivity within the subsystems of the default mode network in PTSD. We found that PTSD was associated with alterations in connectivity involving the MTL subsystem, with reduced correlation between the PCC and the hippocampus and reduced anticorrelation between the vMPFC and the dorsal anterior cingulate cortex. In contrast, no alterations were observed in the dMPFC subsystem of the default mode network. These findings replicate past studies that have found PTSD-related disruptions in PCC-hippocampal connectivity (21, 23) and extend these findings by demonstrating that connectivity alterations are specific to the MTL subsystem. They also extend previous work showing altered connectivity between the default mode and salience networks (23) by demonstrating that cross-network alterations likewise are limited to the MTL subsystem of the default mode network.

Alterations in the MTL subsystem may contribute to impairments in contextual fear extinction processes in PTSD, as the hippocampus is involved in contextual fear extinction recall (16) and is less active during fear extinction recall in PTSD (15). The PCC has also been associated with contextual processing (52, 53) and plays a role in extinction recall (17). Therefore, it is possible that the disrupted functional connectivity between the PCC and the MTL subsystem serves as a mechanism by which contextual fear extinction processes are impaired in PTSD.

Consistent with this notion, we found that functional connectivity between the PCC and hippocampus was associated with avoidance/numbing symptoms (i.e., avoidance of thoughts and feelings associated with the trauma, avoidance of reminders of the trauma, or inability to recall an important aspect of the trauma), such that PTSD individuals with reduced PCC-hippocampal functional connectivity exhibited more symptoms. The association between avoidance and the MTL subsystem reported here is in line with the findings of Sripada et al. (54), who reported a link between vMPFC-hippocampal connectivity and PTSD symptomatology. Together, these studies point to the importance of the MTL subsystem in avoidance symptoms. A recent animal lesion study examining approach-avoidance conflict

found that rats with ventral hippocampal lesions were significantly more avoidant of a previously learned aversive cue during the extinction phase than sham controls (55), suggesting that disruptions in the hippocampus and associated alterations in extinction recall may contribute to increased avoidance behaviors. In light of the notion that both the PCC and hippocampus may be important for fear extinction, we suggest that disruptions in the functional connectivity between the PCC and hippocampus may disrupt extinction recall and consequently, lead to avoidance behavior.

Alterations in connectivity between the PCC and the MTL subsystem may also disrupt autobiographical memory processes and thereby contribute to the maintenance of PTSD. The medial prefrontal cortex, hippocampus and PCC are critical components of an autobiographical retrieval network (56–58). Prior work suggests that activity in the PCC and hippocampus is associated with successful retrieval of autobiographical events (56, 58, 59), and notably, that the functional connectivity between the PCC and hippocampus is involved in episodic autobiographical remembering (60, 61). Individuals with PTSD tend to retrieve overgeneral autobiographical memories, i.e., generic memories that are devoid of specific details (62–64). This tendency to retrieve overgeneral memories may be associated with alterations in a PCC-hippocampal pathway that is important for retrieving details of autobiographical memories. Moreover, as overgeneral memory is associated with avoidance (64–66), this could also explain the observed relationship between PCC-hippocampal connectivity and avoidance/numbing symptoms.

Interestingly, recent work by King and colleagues (26) found that improvement in avoidance symptoms in PTSD after a mindfulness therapy program was associated with increased PCC-dorsolateral prefrontal cortex connectivity. This finding may suggest that a therapeutic intervention that engages the central executive network, such as mindfulness, may mitigate avoidance symptoms and, speculatively, may normalize the aberrant connectivity observed between the PCC and hippocampus in our study. However, more research is needed to further investigate this possibility.

In addition to reduced functional connectivity within the MTL subsystem, our findings revealed disrupted functional connectivity between this subsystem and a region outside of the default mode network. Specifically, we found decreased anticorrelation between the vMPFC and dorsal anterior cingulate cortex, a region that is commonly associated with the salience network (67, 68). The salience network is a network of paralimbic structures that is involved in externally-directed task engagement and is important for identifying and responding to salient stimuli (68). The dorsal anterior cingulate cortex has been implicated in fear expression (69, 70) and is hyper-responsive in PTSD (1, 5, 71, 72), and the vMPFC has also been associated with fear expression, with disruptions leading to an exaggerated fear response (2, 4). Although alterations between the vMPFC and the amygdala have been postulated as a critical mechanism for exaggerated fear response and hypervigilance (73–75), our results suggest that disrupted functional connectivity between the vMPFC and dorsal anterior cingulate cortex may similarly be involved. Surprisingly, these findings were not associated with hyperarousal symptoms, suggesting that vMPFC-dorsal anterior cingulate cortex connectivity may not be directly involved in fear-related behavioral manifestations.

Interestingly, in a sample of youth with PTSD, connectivity between the default mode network and salience network was positively related to feelings of hopelessness, a finding interpreted to suggest that anticorrelation might be associated with the perception of symptom controllability when engaged in external tasks (76). It is interesting to consider the possibility that the reduced anticorrelation observed in the current study might similarly reflect the subjective interpretation of hypervigilance, although parallels between adult and pediatric PTSD should be drawn cautiously given evidence for increased cross-network anticorrelations in youth with PTSD, a finding thought to reflect a compensatory mechanism (76).

PTSD and depression were highly comorbid in our sample, raising a question concerning the specificity of our findings. Complicating this question, PTSD encompasses an array of symptoms, some shared with depression and some unique. Indeed, some have argued that PTSD and depression in the aftermath of trauma are best thought of as a single, general traumatic stress response (77). Nonetheless, when depression was included in the model, PTSD remained significantly associated with PCC-hippocampal and vMPFC-dorsal anterior cingulate cortex connectivity, suggesting that posterior default mode network disruptions may be specific to PTSD.

Additionally, our study included a number of participants with a history of deployment-related mTBI, raising the possibility that mTBI contributed to the findings. However, mTBI was not significantly associated with PCC-hippocampal or vMPFC-dorsal anterior cingulate cortex functional connectivity, suggesting that disruptions in the MTL subsystem of the default mode network are not the result of mTBI. Nonetheless, more work is needed to further investigate whether mTBI may moderate functional connectivity in PTSD.

Some limitations of the current study should be noted. First, our sample was predominantly male and consisted of Veterans who had sustained combat-related trauma. It is unknown whether the findings would generalize to females and non-combat related PTSD samples. Recent studies suggest that disruptions in default mode network connectivity are also present in non-combat related PTSD samples (21, 33), although it is unknown whether the disruption is limited to a particular default mode subsystem. Second, this study focused on the default mode network subsystems in PTSD and did not examine within network alterations in other resting state networks. There is evidence that PTSD is associated with functional connectivity alterations within the salience (23, 27, 54) and central executive (22, 36, 78) networks, and as such, it will be important for future work to examine the contributions of disruptions in these networks to clinical presentations of the disorder. Third, the current study used a liberal cluster defining threshold of $P < 0.01$. However, recent evidence suggests that the family wise error was likely reduced by virtue of the fact that the between-subject variance in resting state data tends to be overestimated in FLAME, hence resulting in a conservative cluster-wise inference (50). Moreover, results were confirmed using AFNI's autocorrelation feature that accounts for heavier Gaussian tails. Nonetheless, it will be important for future studies to validate these findings with other statistical methods. Lastly, this is a cross-sectional study and does not allow for causal inferences. Longitudinal research is needed to determine whether these functional connectivity disruptions reflect risk factors or consequences of PTSD.

In summary, we report functional connectivity alterations selective to the MTL subsystem of the default mode network in PTSD. Specifically, individuals with PTSD compared to trauma-exposed controls showed reduced functional connectivity between the PCC and the hippocampus, and this altered connectivity was associated with increased avoidance/numbing symptoms. In addition, we found disruptions in functional connectivity between the MTL subsystem and the salience network, providing evidence for diminished network segregation in PTSD. Together, these results suggest that disruptions in the MTL subsystem may be an important factor in PTSD pathology and symptomatology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Functional connectivity analyses of individuals with PTSD, trauma-exposed controls, and group comparisons. Color scale indicates Z-score associated with positive functional connectivity (red-yellow) or negative functional connectivity (blue-light blue). **A.** Individuals with PTSD showed reduced positive functional connectivity between the PCC seed and the hippocampus. There were no significant group differences in functional connectivity between the aMPFC (**B.**) or dMPFC (**C.**) seeds and any region within the brain. **D.** Individuals with PTSD showed reduced anticorrelation between the vMPFC and the dorsal anterior cingulate cortex. aMPFC=anterior medial prefrontal cortex; dMPFC=dorsomedial prefrontal cortex; L=left; PCC=posterior cingulate cortex; PTSD=posttraumatic stress disorder; R=right; vMPFC=ventromedial prefrontal cortex.

Figure 2.

The association between CAPS avoidance/numbing score and functional connectivity between the PCC and hippocampus in individuals with PTSD (**A**) and trauma exposed controls (**B**). CAPS=Clinician-Administered PTSD Scale; PCC=posterior cingulate cortex; PTSD=posttraumatic stress disorder.

Table 1

Demographic and clinical characteristics.

Variable	Controls (<i>n</i> =44)	PTSD (<i>n</i> =69)	Group Comparison
Age in years, <i>M</i> (<i>SD</i>)	29.2 (6.1)	29.4 (6.4)	Mann-Whitney <i>U</i> =1498.5, <i>P</i> =0.9
Males, <i>no.</i> (%)	40 (90.9)	67 (97.1)	$\chi^2(1)=2.1$, <i>P</i> >0.1
WTAR Z-score, <i>M</i> (<i>SD</i>)	0.4 (0.9)	0.4 (0.7)	Mann-Whitney <i>U</i> =1434.5, <i>P</i> =0.6
Current alcoholic drinks per week, <i>M</i> (<i>SD</i>)	4.5 (5.9)	5.8 (8.9)	Mann-Whitney <i>U</i> =1398.5, <i>P</i> =0.5
CAPS total, <i>M</i> (<i>SD</i>)	25.0 (14.1)	70.4 (18.1)	<i>t</i> (111)=-14.1, <i>P</i> <0.001
CAPS re-experiencing, <i>M</i> (<i>SD</i>)	6.8 (5.8)	18.5 (7.8)	<i>t</i> (109)=-8.5, <i>P</i> <0.001
CAPS avoidance/numbing, <i>M</i> (<i>SD</i>)	7.4 (6.8)	27.0 (9.2)	<i>t</i> (107.3)=-12.9, <i>P</i> <0.001
CAPS hyperarousal, <i>M</i> (<i>SD</i>)	10.8 (7.0)	24.2 (6.6)	<i>t</i> (109)=-10.2, <i>P</i> <0.001
mTBI diagnosis, <i>no.</i> (%)	14 (31.8)	45 (65.2)	$\chi^2(1)=12.0$, <i>P</i> =0.001
Combat exposure, <i>M</i> (<i>SD</i>)	7.6 (4.3)	10.6 (3.1)	<i>t</i> (72.1)=-4.0, <i>P</i> <0.001
Beck Depression Inventory-II, <i>M</i> (<i>SD</i>)	10.0 (8.3)	22.0 (10.2)	<i>t</i> (111)=-6.6, <i>P</i> <0.001
Medication, <i>no.</i> (%)	9 (20.5)	35 (50.7)	$\chi^2(1)=10.4$, <i>P</i> =0.001
Childhood trauma exposure, <i>no.</i> (%)	5 (11.4)	9 (13.0)	$\chi^2(1)=0.08$, <i>P</i> =0.8

Note: For ease of interpretation, we report the means and standard deviations 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.

Table 2

Differences in functional connectivity between PTSD and control participants.

Seed	Contrast	Z Max	X	Y	Z	Brain Region
Left PCC	PTSD < Controls	4.05	28	-38	2	Right Parahippocampus/ Hippocampus
		3.67	18	-54	28	Right PCC *
vMPFC	PTSD < Controls	4.87	26	58	-4	Right Frontal Pole *
		4.35	6	30	30	Right Dorsal Anterior Cingulate Cortex

Note: Coordinates are in Montreal Neurological Institute (MNI) space. The PTSD < Controls contrast in the vMPFC seed reflects a reduced anticorrelation in the PTSD group. Only peak coordinates of clusters are listed. Subclusters are not reported. aMPFC= anterior medial prefrontal cortex; PCC= posterior cingulate cortex; vMPFC= ventromedial prefrontal cortex.

* =did not survive using AFNI's autocorrelation option and Monte Carlo α simulation.