

Regional Prefrontal Resting-State Functional Connectivity in Posttraumatic Stress Disorder

Elizabeth A. Olson, Roselinde H. Kaiser, Diego A. Pizzagalli, Scott L. Rauch, and Isabelle M. Rosso

ABSTRACT

BACKGROUND: Prefrontal subregions, including the ventromedial prefrontal cortex (PFC), dorsomedial PFC, and dorsolateral PFC (DLPFC), are differentially implicated in the pathophysiology of posttraumatic stress disorder (PTSD), though few existing studies have examined subregional differences in resting-state functional connectivity (rsFC). We hypothesized that PTSD would involve weaker positive rsFC between ventromedial PFC, dorsomedial PFC, and other default mode network regions and increased negative rsFC between DLPFC and posterior default mode network regions. Additionally, we hypothesized that prefrontal regions exhibiting group differences in rsFC would be characterized by alterations in cortical thickness.

METHODS: Participants included 36 healthy control subjects, 30 trauma-exposed control subjects, and 21 individuals with current DSM-IV PTSD resulting from community-acquired trauma. Participants completed the Clinician Administered PTSD Scale, questionnaires (Childhood Trauma Questionnaire, Adverse Childhood Events, Life Events Checklist, Beck Depression Inventory), structural neuroimaging, and resting-state functional magnetic resonance imaging. rsFC of DLPFC, ventromedial PFC, and dorsomedial PFC seeds was evaluated in SPM12 and CONN. Cortical thickness for regions with significant rsFC findings was assessed using FreeSurfer.

RESULTS: Relative to both healthy control and trauma-exposed control subjects, individuals with PTSD showed increased negative rsFC between the DLPFC and a region of precuneus. This finding was associated with increased overall symptom severity but not with trauma load or childhood trauma exposure. Greater negative DLPFC-precuneus connectivity was associated with greater bilateral precuneus thickness.

CONCLUSIONS: Given participation of precuneus subregions in the central executive network, increased anti-correlation between right DLPFC and precuneus in this sample may reflect increased opposition between anterior and posterior central executive network hubs in PTSD.

Keywords: Cortical thickness, Functional connectivity, Posttraumatic stress disorder, Precuneus, Prefrontal cortex, Resting state

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Early task-based functional neuroimaging studies in post-traumatic stress disorder (PTSD) established the critical role of medial prefrontal cortex (PFC) hypoactivity in insufficient inhibition of hyperresponsive amygdala output (1,2), resulting in hyperarousal and re-experiencing symptoms. While these relationships are well established during affective processing tasks, alterations in resting-state functional connectivity (rsFC) in PTSD have also received increasing attention. rsFC measures the coherence of brain region activity in the absence of explicit task-related demands and in healthy individuals is correlated with neural activity during task performance (3) as well as important functional outcomes, including emotional perception and regulation (4) and cognitive performance (5,6).

Many rsFC studies in PTSD have focused on within-network and cross-network coherence in three major resting-state networks, consistent with Menon's (7) triple network model articulating how aberrant interactions between three large-

scale resting-state networks contribute to psychopathology. According to Menon's model and spatial organization of these networks, the first is the default mode network (DMN), with central hubs in the posterior cingulate cortex (PCC) and medial PFC; this network is active in the absence of explicit task demands and is associated with functions including self-referential processing (8,9). The second is the salience network (also known as salience and emotional network [SEN]), with hubs in the dorsal anterior cingulate cortex and anterior insula, involved in allocating cognitive resources to other large-scale networks on the basis of salient internal or external events (10,11). Of note, in this model, the SEN also includes the amygdala and the substantia nigra/ventral tegmental area (7,12). The third key network is the central executive network (CEN), with hubs in the dorsolateral PFC (DLPFC) and posterior parietal cortex, involved in working memory and execution of goal-directed behavior (11,13).

Regional Prefrontal rsFC in PTSD

Extensive focus on these core hubs within the PTSD rsFC literature may result in insufficient attention to regionally nuanced findings. This may be particularly critical for dysfunction of the PFC, for which there is evidence that collapsing across functionally differentiated subregions may obscure important results. For example, recent work in healthy adults indicates that the frontal lobe component of the DMN subdivides into a ventromedial PFC (VMPFC) component (which is functionally connected to medial temporal lobe regions and plays a role in learning and memory) and a dorsomedial PFC (DMPFC) component (which is involved in mentalizing and self-reflection) (14). Differential contributions of DMPFC and VMPFC to fear and anxiety broadly (15,16) and to PTSD specifically (17,18) have been identified, but few existing resting-state studies in PTSD examine connectivity from these prefrontal subregions separately. Given the functional roles of these subregions in processes impaired in PTSD—including the role of the VMPFC in fear extinction learning and recall (19,20) and reward valuation (21) and the role of the DMPFC in mentalizing (22)—targeting these regions separately for resting-state analyses could be critical. Additionally, PTSD rsFC studies examining medial PFC connectivity often do not concurrently probe alterations in lateral PFC connectivity. Evaluating medial and lateral PFC connectivity in the same sample is particularly important because of their potential interactions. PTSD has been associated with DLPFC hypoactivation during cognitive reappraisal (23) and executive control tasks (24), but there are relatively few studies of intrinsic rsFC of the DLPFC in PTSD. In this article, we summarize the existing literature on dysfunction in prefrontal rsFC from three prefrontal regions implicated in cognitive and emotional dysfunction in PTSD: the VMPFC, DMPFC, and DLPFC.

Ventromedial PFC

Many previous reports of rsFC in PTSD have focused on a medial prefrontal region located in the VMPFC (25) that overlaps with the prototypical DMN but may also extend into the so-called affective network (26). Reduced connectivity between the VMPFC and DMN regions (including PCC and right superior parietal lobule) has been demonstrated in individuals with PTSD compared with healthy control subjects (27). In addition to this hypoconnectivity between areas of VMPFC and DMN regions, PTSD may involve abnormal cross-network coupling of VMPFC with salience network regions including the dorsal anterior cingulate cortex (18). Relatedly, rsFC between VMPFC and the amygdala has been implicated in PTSD; across a mixed diagnostic sample of individuals with depression and PTSD, anxiety was associated with hyperconnectivity between the VMPFC and the amygdala (28). Interestingly, healthy adults with greater connectivity between VMPFC and regions of the salience and central executive networks (i.e., greater between-network connection strength) show worse attentional performance (poor distractor suppression), a cognitive deficit seen in PTSD (29). From a neurodevelopmental perspective, there is evidence that, in contrast to in adult PTSD, pediatric PTSD may be associated with hyperconnectivity between the VMPFC and other DMN regions (30). To summarize, the existing literature suggests that PTSD involves hypoconnectivity between VMPFC and DMN as well as hyperconnectivity between

VMPFC and SEN regions, though the developmental timing of PTSD onset may influence this pattern.

Dorsomedial PFC

The DMPFC is a region of the DMN that is functionally involved in mentalizing and self-reflection (14,31). In PTSD, DMPFC hyperconnectivity with the basolateral amygdala has been demonstrated (32), perhaps reflecting intrusion of amygdala-driven fear-related content during self-reflective thought. Increased negative connectivity between the amygdala/hippocampus and the DMPFC occurs in the context of increasing childhood trauma exposure and combat exposure, increasing positive amygdala/hippocampus to DMPFC connectivity scales with overall PTSD symptom severity (33). In a previous rsFC study, we found that increased right DMPFC–nucleus accumbens functional connectivity was associated with greater anhedonia in trauma-exposed adults (34), consistent with the perspective that DMPFC hyperconnectivity with regions outside the DMN may contribute to dimensional features of trauma-related psychopathology. Together, these findings suggest that DMPFC hyperconnectivity may be an important feature in PTSD and may be related to symptoms including alterations in reward processing.

Dorsolateral PFC

Overall, prior PTSD rsFC literature on VMPFC and DMPFC connectivity suggests that PTSD is associated with hyperconnectivity between these midline regions and regions outside the DMN, including SEN components. In contrast, studies of DLPFC connectivity in PTSD have generally demonstrated that PTSD involves hypoconnectivity between DLPFC and SEN regions (35), including reduced rsFC between the DLPFC and the anterior insula (36). Similarly, in a transdiagnostic sample of individuals with depression or PTSD, depressive symptom severity was associated with hypoconnectivity between the DLPFC and the amygdala (28). This hypoconnectivity is presumed to reflect insufficient goal-directed cognitive regulation of affective and attentional processes. PTSD also is associated with decreased connectivity between lateral PFC and DMN regions (37); for instance, re-experiencing symptom severity is associated with lower degree (i.e., weaker network influence) between the right DLPFC and the right hippocampus (38). Consistent with the hypothesis that PTSD involves hypoconnectivity between DLPFC and DMN regions, successful treatment via mindfulness-based exposure therapy and associated reduction in avoidant and hyperarousal symptoms is associated with increased rsFC between DLPFC and DMN nodes including the PCC (39). While only a few studies to date have examined DLPFC-DMN rsFC in PTSD, the existing findings suggest that PTSD may involve altered DLPFC modulation of DMN circuits involved in autobiographical memory. This stands in contrast to the bulk of findings in major depressive disorder, which suggest hyperconnectivity (namely, reduced anticorrelations in activity) between frontal control network regions (including DLPFC) and DMN (40).

Limitations of Existing rsFC Prefrontal Literature

Most of the existing prefrontal rsFC literature in PTSD has focused on individuals with PTSD with combat trauma and has

been conducted in predominantly male samples (e.g., $\geq 85\%$ men) (18,27,29,33,36–39). Studies that include women have tended to focus on single-incident, noninterpersonal traumas, such as natural disasters (41–43). One study that did include female subjects was conducted in adolescents and demonstrated strikingly different findings than existing studies in adult samples—i.e., no indication that PTSD involves hypoconnectivity within the DMN (30). Whereas the authors primarily interpreted their divergent findings in terms of possible differences between pediatric-onset and adult-onset PTSD, it is also possible that the difference in sex distribution of the samples may have contributed.

Linking Structural Morphometry and Functional Connectivity

Establishing relationships between alterations in structure and function is an important step in bridging the structural and functional psychopathology neuroimaging literature. There is evidence that regional prefrontal group differences in cortical thicknesses are associated with alterations in rsFC in major depressive disorder (44) and with altered resting-state activity in PTSD (45). These and other findings (46) suggest possible associations between altered cortical thickness and rsFC, though, to our knowledge, there have not been previous investigations linking rsFC and cortical thickness within a PTSD sample.

Prefrontal Effects of PTSD Versus Early Life Stress

One additional feature that is not frequently evaluated in studies of rsFC in combat populations is the possible contribution of effects related to prior childhood and/or adolescent adversity or trauma exposure. Early life stress (ELS) exposure is associated with alterations in prefrontal rsFC, including increased negative connectivity between the DLPFC and precuneus/inferior parietal lobule (47). This increased anticorrelation between DLPFC and precuneus may reflect increased dissociation between DMN and CEN in the context of ELS: the opposite of the above-described pattern for PTSD. Similarly, childhood maltreatment severity is associated with increased anticorrelation between SEN seeds (amygdala, hippocampus) and VMPFC, DMPFC, and DLPFC (33). Increased negative rsFC between the amygdala and the DLPFC also was identified in women exposed to threat-related ELS (48). The increased DLPFC anticorrelation has been characterized as a possible compensatory mechanism involving increased voluntary emotional regulation (33). However, participants in these studies did not have PTSD related to childhood abuse. Therefore, it is unclear whether increased prefrontal anticorrelations are a scar related to ELS exposure or a feature associated with resilience to that exposure. These findings also contrast with findings described above in non-ELS samples, which generally show DLPFC hypoconnectivity in the context of PTSD. The effect of stress/trauma exposure on prefrontal rsFC may depend on the developmental timing of the stress exposure; for instance, childhood and/or adolescent trauma exposure may lead to heightened differentiation between DMN and CEN, whereas adult trauma exposure may lead to a loss of cross-network differentiation.

Summary and Hypotheses

The VMPFC, DMPFC, and DLPFC are differentially implicated in cognitive and emotional functioning in PTSD. The existing rsFC literature suggests that the VMPFC and DMPFC may demonstrate hypoconnectivity with DMN regions and hyperconnectivity with SEN regions, including the amygdala; DMPFC hyperconnectivity may scale with trauma load and dimensional features, such as anhedonia. In contrast, the existing PTSD rsFC literature suggests that the DLPFC may demonstrate hypoconnectivity with SEN regions (amygdala, anterior insula) as well as hypoconnectivity with the DMN. Importantly, these patterns have primarily been established in combat samples, and extension to community-based samples (including samples with a higher proportion of women) is a critical next step. Community-based PTSD samples tend to include balanced sex distributions as well as subjects with childhood trauma exposure. Based on the existing prefrontal rsFC literature, we hypothesized that relative to both trauma-exposed control (TENC) subjects and non-trauma-exposed healthy control (HC) subjects, individuals with PTSD would demonstrate reduced within-network connectivity from VMPFC and DMPFC seeds to other DMN regions and increased cross-network connectivity from VMPFC and DMPFC seeds to salience network regions. Based on the adult PTSD literature in combat samples, we anticipated hypoconnectivity between DLPFC and DMN regions, though in this sample of subjects with significant childhood trauma, we also considered the possibility of increased negative connectivity between DLPFC and posterior DMN regions. Finally, we hypothesized that prefrontal regions demonstrating group differences in rsFC would also demonstrate alterations in cortical thickness, consistent with prior demonstrations of associations between cortical thickness and rsFC.

METHODS AND MATERIALS

Participants

All participants provided written informed consent, and study procedures were approved by the Partners Human Research Committee. The study included 87 participants (36 HC subjects, 30 TENC subjects, 21 individuals with current PTSD) (Table 1). Our laboratory previously published findings related to rsFC of the nucleus accumbens in relation to anhedonia in the TENC participants and participants with PTSD (34). Participants were recruited from the Boston area via advertisements. Inclusion criteria included right-handedness, age between 20 and 50 years, and trauma exposure appropriate to group (for detailed inclusion and exclusion criteria, see Supplement). During the interview, all TENC subjects endorsed having experienced at least one event meeting DSM-IV PTSD criterion A, whereas HC subjects reported no history of events meeting criterion A.

Clinical Symptom and Trauma Questionnaires

PTSD Symptom Ratings: Clinician Administered PTSD Scale, Current and Lifetime Version. Total current DSM-IV PTSD severity scores and subscale scores for re-experiencing, avoidance, and hyperarousal were generated

Table 1. Demographics and Clinical Variables: Group Characteristics

	HC (<i>n</i> = 36)	TENC (<i>n</i> = 30)	PTSD (<i>n</i> = 21)	Group Difference
Age, Years	32.81 (9.03)	30.99 (7.91)	34.11 (6.94)	$F_{2,84} = 0.942$, ns
Sex, F/M	19/17	18/12	12/9	$\chi^2_{2,87} = 0.838$, ns
CAPS Re-experiencing	—	2.43 (3.78)	14.67 (7.00)	$t_{28,202} = -7.30$, $p < .001^a$
CAPS Avoidance	—	3.37 (5.20)	27.57 (8.94)	$t_{29,438} = -11.16$, $p < .001^a$
CAPS Hyperarousal	—	2.37 (3.72)	17.43 (6.42)	$t_{29,391} = -9.68$, $p < .001^a$
CAPS Total	—	8.17 (9.87)	59.67 (18.75)	$t_{27,796} = -11.52$, $p < .001^a$
CTQ Emotional Abuse ^{b,c}	6.14 (1.76)	9.45 (4.04)	14.48 (7.43)	$F_{2,35,516} = 19.62$, $p < .001^a$
CTQ Physical Abuse ^d	5.64 (1.05)	8.20 (4.00)	10.05 (4.78)	$F_{2,33,930} = 13.71$, $p < .001^a$
CTQ Sexual Abuse ^{c,e}	5.25 (1.50)	7.14 (4.44)	9.05 (6.26)	$F_{2,34,394} = 5.74$, $p = .007^a$
CTQ Emotional Neglect ^d	7.78 (3.16)	11.10 (4.85)	14.14 (5.99)	$F_{2,42,038} = 12.87$, $p < .001^a$
CTQ Physical Neglect ^b	5.44 (0.10)	6.73 (2.16)	9.14 (3.57)	$F_{2,36,785} = 14.02$, $p < .001^a$
ACE Total ^d	0.63 (0.81)	3.00 (1.89)	4.67 (2.85)	$F_{2,36,499} = 36.81$, $p < .001^a$
LEC Total ^b	2.61 (2.63)	6.27 (2.99)	9.10 (3.56)	$F_{2,84} = 30.85$, $p < .001$
BDI Total ^{b,f}	0.64 (1.22)	6.47 (7.02)	20.30 (11.28)	$F_{2,31,444} = 39.03$, $p < .001^a$
Motion, Number of Flagged Scans	6.44 (5.84)	7.20 (5.71)	6.57 (5.52)	$F_{2,84} = 0.154$, ns

Values are mean (SD) or *n*.

ACE, Adverse Childhood Experiences scale; BDI, Beck Depression Inventory; CAPS, Clinician Administered PTSD Scale; CTQ, Childhood Trauma Questionnaire; F, female; HC, healthy control; LEC, Life Experiences Checklist; M, male; ns, not significant; PTSD, posttraumatic stress disorder; TENC, trauma-exposed control.

^aTests adjusted for nonhomogeneity of variances, e.g., Welch test for analysis of variance, Games-Howell post hoc test.

^bHC group < TENC group < PTSD group.

^cFor CTQ, 1 missing data point in TENC group (*n* = 29).

^dHC group < PTSD group, HC group < TENC group, no significant differences between TENC group and PTSD group.

^eHC group < PTSD group, no significant differences between TENC group and HC or PTSD group.

^fFor BDI, 1 missing data point in PTSD group (*n* = 20).

via structured interview using the Clinician Administered PTSD Scale (CAPS), Current and Lifetime Version (49).

Childhood Trauma Exposure: Childhood Trauma Questionnaire and Adverse Childhood Experiences.

The Childhood Trauma Questionnaire (50) is a 28-item self-report measure of childhood trauma exposure, including emotional abuse and neglect, physical abuse and neglect, and sexual abuse. The Adverse Childhood Experiences scale (51) is a 10-item self-report measure of childhood abuse, neglect, and stressful life experiences.

Trauma Load: Life Experiences Checklist. The Life Experiences Checklist (52) was used as a measure of trauma load (number of personally experienced plus personally witnessed lifetime events).

Depression: Beck Depression Inventory. The Beck Depression Inventory, version 1A (53), total score was used as a measure of depression severity.

Magnetic Resonance Imaging Acquisition and Analysis

Full details of image acquisition and preprocessing are described in our previous article (34) and available in the Supplement. Briefly, scans were acquired on a 3T Tim Trio scanner (Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil. Structural T1-weighted magnetization prepared rapid acquisition gradient-echo images were collected over 128 sagittal slices (repetition time = 2530 ms, echo time = 3.31 ms, flip angle = 7°, 256 × 256 matrix), voxel

size = 1.3 × 1.0 × 1.3 mm³. An eyes-open resting-state scan was acquired; 180 T2-weighted echo-planar images were collected over 34 transverse interleaved slices (repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°), voxel size = 3.5 × 3.5 × 3.5 mm, field of view = 224 mm. SPM12 Revision Number 6225 was used for data preprocessing in MATLAB R2014a (The MathWorks, Inc., Natick, MA). Standard processing steps were performed in CONN version 15.h (NeuroImaging Tools & Resources Collaboratory; <https://www.nitrc.org/projects/conn>), including denoising via CompCor and bandpass filtering (0.008–0.09 Hz).

Resting-State Analysis

To define the peak coordinates for the DLPFC, DMPFC, and VMPFC regions of interest, we drew from the normative cognitive neuroscience literature. Following Baumgartner *et al.* (54), we used the following peak coordinates: DLPFC (peak for a control-related region in Brodmann area 9: *x* = ±39, *y* = 37, *z* = 26); DMPFC (peak for a mentalizing-related region: −3, 48, 30); posterior VMPFC (peak for a reward valuation-related region: 2, 41, −6). Using FSL, spheres of 5-mm radius were dilated at these peak coordinates and binarized (Supplemental Figure S1). The Pearson correlations between the time course of each seed (left and right DLPFC, DMPFC, VMPFC) and the time course of every other voxel in the brain were computed and transformed using Fisher's *z*. For the second-level analysis, first-level maps were entered into whole-brain regression analyses. For each seed, we performed an analysis of covariance to test for a main effect of group (PTSD, TENC, HC), controlling for age and sex. Results of this *F* test were thresholded at $p < .001$ (uncorrected height threshold),

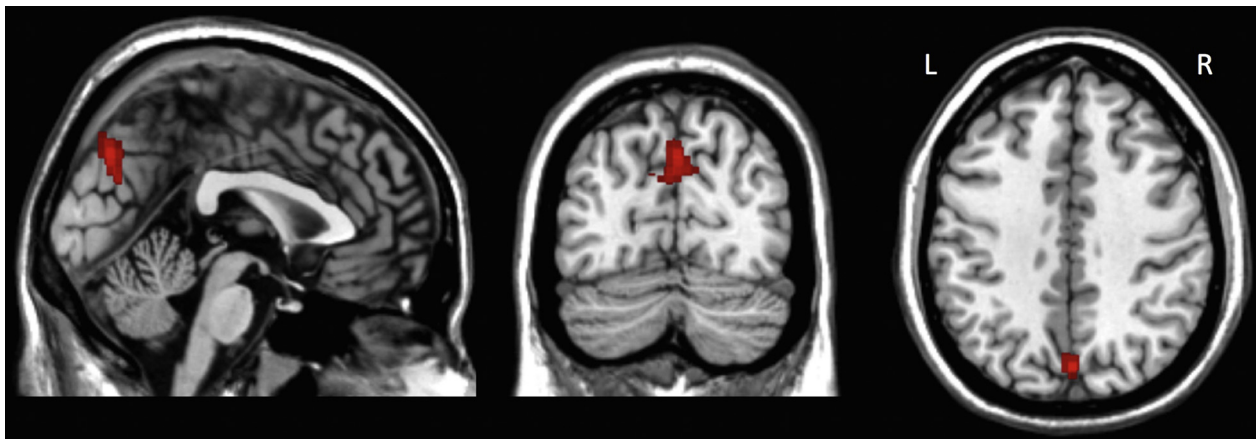


Figure 1. Region in precuneus with significant group difference in right dorsolateral prefrontal cortex resting-state functional connectivity. $k = 212$ voxels, false discovery rate corrected $p = .000064$, peak coordinates = $(+8, -72, +32)$. L, left; R, right.

$p < .05$, false discovery rate–corrected cluster-size threshold. To correct for multiple comparisons (analyses initiated from four seeds), results were considered significant at Bonferroni-corrected $p < .0125$ ($0.05/4$). A whole-brain analysis was performed from each seed to allow for the possibility of significant results outside the canonical rsFC networks (DMN, SEN, CEN). Connectivity values (Fisher's r to z) were extracted from significant F test clusters for correlations with symptom and trauma scores.

Cortical Thickness

FreeSurfer version 5.3.0 was used for cortical surface reconstruction using a standard processing pipeline. Cortical thickness measurements were taken by averaging the distance from the pial surface to the gray-white interface. FreeSurfer segmentations were manually inspected and edited by the first author (EAO) in accordance with recommended guidelines. Cortical thickness of regions demonstrating significant group differences in the resting-state analyses was derived (see Supplement for region of interest derivation).

RESULTS

Group Differences in rsFC

There were no significant diagnostic group differences in rsFC from the DMPFC, VMPFC, or left DLPFC seeds. In contrast, there was a significant group difference in rsFC from the right DLPFC seed to a region in the bilateral precuneus (212 voxels, cluster false discovery rate corrected $p = .000064$) (Figure 1). Subsequent pairwise comparison analyses showed lower rsFC values (increased negative rsFC) in the PTSD group compared with both the HC and the TENC groups, with no significant difference between the HC and TENC groups (Figure 2).

Correlations With Cortical Thickness

Across the whole sample, controlling for age and sex, greater negative DLPFC-precuneus connectivity was associated with greater precuneus thickness on the right (partial $r_{83} = -.218$, $p = .045$) and on the left (partial $r_{83} = -.223$, $p = .040$). There

were no group differences in precuneus thickness on the right ($F_{2,80} = 0.016$, $p = .984$) or the left ($F_{2,80} = 0.146$, $p = .864$) or in DLPFC thickness on the right ($F_{2,80} = 0.265$, $p = .768$) or the left ($F_{2,80} = 0.085$, $p = .918$). DLPFC thickness was not significantly correlated with DLPFC-precuneus rsFC.

Relationships With Core Clinical Outcomes (CAPS Scores)

Within the PTSD group, controlling for age and sex, greater negative DLPFC-precuneus connectivity was associated with greater total CAPS scores (partial $r_{17} = -.463$, $p = .046$) and greater CAPS avoidance symptoms (partial $r_{17} = -.485$, $p = .035$) (Figure 3); see Supplemental Table S1 for partial correlations between right DLPFC-precuneus rsFC and symptom scores within the PTSD sample.

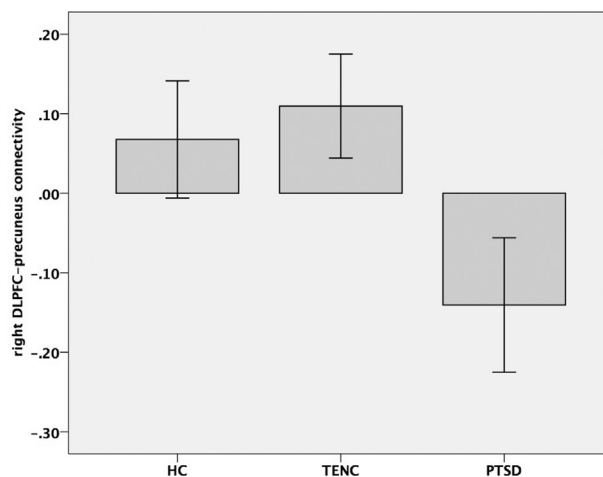


Figure 2. Group comparison of right dorsolateral prefrontal cortex (DLPFC)-precuneus resting-state functional connectivity values. Note that resting-state functional connectivity values in this graph are raw (not corrected for age and sex). Error bars = 95% confidence interval. HC, healthy control; PTSD, posttraumatic stress disorder; TENC, trauma-exposed control.

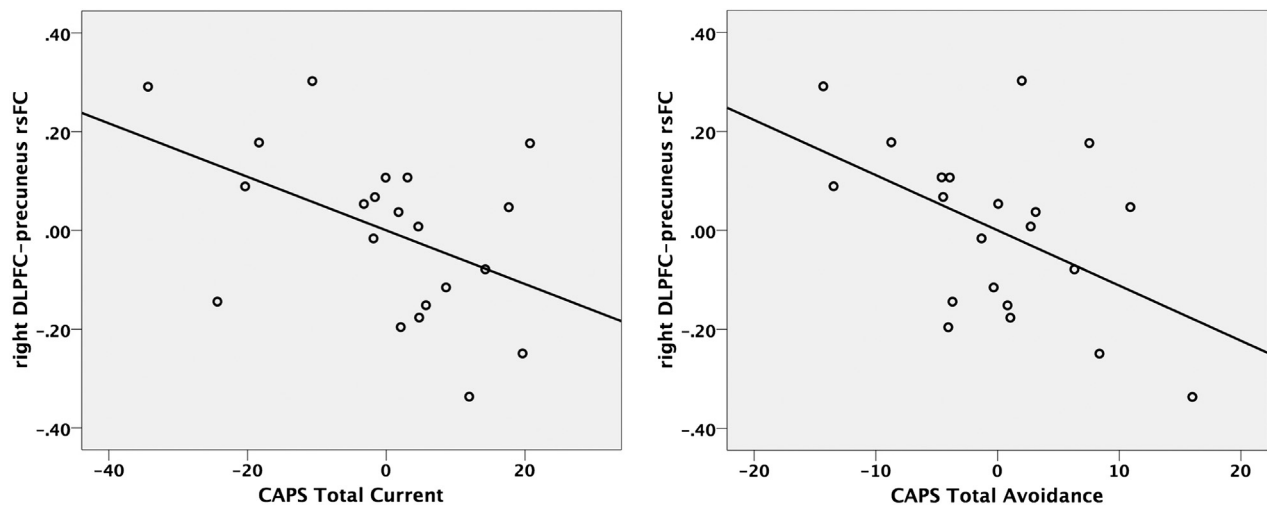


Figure 3. Partial correlation of Clinician Administered PTSD Scale (CAPS) total symptom scores (left panel) and CAPS avoidance scores (right panel) with right dorsolateral prefrontal cortex (DLPFC)–precuneus resting-state functional connectivity (rsFC) in posttraumatic stress disorder group, controlling for age and sex.

Relationships With Childhood Trauma Exposure, Trauma Load, and Depression

As shown in Table 1, both the PTSD and the TENC groups reported elevated exposure to childhood adverse events compared with the HC group using the self-report measures. Correlations within the PTSD group were not significant for the relationship between DLPFC-precuneus connectivity and Adverse Childhood Experiences total scores (partial $r_{17} = .021$, $p = .931$) or Childhood Trauma Questionnaire subscale scores (partial $r_{17} = -.325$ to $.154$, $p = .175$ to $.739$). In this PTSD sample, there also was no significant relationship between childhood trauma load and current PTSD symptoms: the association was nonsignificant between CAPS total scores and either Adverse Childhood Experiences total scores ($r_{19} = -.185$, $p = .449$) or Childhood Trauma Questionnaire subscale scores ($r_{19} = -.150$ to $.221$, $p = .336$ to $.940$). DLPFC-precuneus rsFC was also not related to lifetime trauma load (Life Experiences Checklist) within the PTSD group (partial $r_{17} = .010$, $p = .968$). The relationship between rsFC and depression (Beck Depression Inventory score) did not reach significance (partial $r_{16} = -.252$, $p = .313$; with one participant missing data on the Beck Depression Inventory).

DISCUSSION

In this community-based sample of adults, adults with PTSD were characterized by increased negative rsFC between the right DLPFC and a bilateral precuneus cluster compared with both TENC and HC subjects. There were no significant differences between TENC and HC subjects. Within the PTSD group, increased negative right DLPFC-precuneus rsFC was associated with greater overall current PTSD symptom scores and with higher current avoidance symptoms but was unrelated to the extent of childhood adverse event exposure. In contrast, there were no significant group differences in rsFC seeded from the left DLPFC, VMPFC, or DMPFC.

Interpretation of the right DLPFC-precuneus rsFC finding is complicated because the participation of the precuneus in resting-state networks is multifaceted. Whereas the precuneus has been described as playing a role in the DMN in some contexts (especially in conjunction with the PCC), in other contexts, it has been characterized as part of the frontoparietal network or CEN (55). In fact, there is evidence that the posterior DMN hub is limited to the PCC and does not extend to the precuneus (56,57). This may be related to differential functional connectivity across precuneus subregions; whereas anterior precuneus and posterior precuneus are functionally connected to sensorimotor and visual regions, respectively, the central precuneus is a cognitive/associative region functionally connected to the DLPFC, DMPFC, and lateral inferior parietal cortex (57).

The present finding is squarely in the precuneus and is not close to the PCC (Supplemental Figure S2), raising the possibility that it localizes to a subregion participating in the CEN as opposed to the DMN. In this case, increased negative rsFC between the right DLPFC and precuneus in PTSD would reflect increased opposition between the anterior and posterior CEN nodes. To confirm this interpretation, we examined placement of our finding relative to an established 17-network model of resting-state networks (26). This analysis confirmed that our result primarily involves voxels that participate in cognitive control as opposed to DMNs (see Supplement). In PTSD, increasing fractionation of the CEN into anterior-posterior subnetworks may have functional implications; for example, hyperactivity among posterior sensory/perceptual integration systems may correspond with decreased activity in goal-oriented PFC regions, consistent with previous documentation of precuneus hyperactivity and DLPFC hypoactivity in PTSD (55). If the precuneus is instead conceptualized as part of the DMN, the present finding would reflect increased opposition between the DMN and CEN. In this case, our finding would be consistent with a recent analysis demonstrating that successful PTSD treatment via exposure therapy (and

associated reduction in avoidant and hyperarousal symptoms) is linked to increased rsFC between DLPFC and DMN nodes, including the PCC (39).

Additionally, in this sample, increased right DLPFC-precuneus negative rsFC was associated with increased precuneus cortical thickness, which could occur in the context of precuneus hyperactivity producing excessive DLPFC inhibition. Precuneus thickness, but not DLPFC thickness, was correlated with DLPFC-precuneus connectivity. Although our cross-sectional data cannot speak to the timing of how this pattern might emerge, one possibility is that individuals with greater precuneus cortical thickness [perhaps associated with well-documented precuneus hyperactivity in PTSD (55)] might be more vulnerable to disruption of precuneus-DLPFC rsFC following trauma exposure. From a clinical perspective, although cognitive performance was not examined in this sample, the observed increased negative rsFC between DLPFC and precuneus may contribute to well-established working memory deficits in PTSD (58).

In this study we have identified the same rsFC pattern as was demonstrated in a sample without psychopathology but with ELS (47). Our identification of this pattern in a sample with PTSD suggests that the observed difference in DLPFC-parietal connectivity is not a feature associated with resilience. Because the vast majority of our individuals with PTSD did report childhood trauma exposure, we are not able to differentiate specific effects related to the timing of trauma exposure (during childhood vs. adulthood). Increased DLPFC-precuneus negative rsFC may thus be a feature that arises in the context of childhood and/or adolescent trauma exposure, though in this sample the rsFC finding did not scale with childhood trauma load.

We did not find group differences in DMPFC or VMPFC rsFC; this could be related to our use of a whole-brain search strategy with particularly stringent statistical thresholds. Alternatively, this may be related to the seed selection in this analysis; investigating other targeted regions of DMPFC or VMPFC as seeds may reveal other functional circuits that are disrupted in PTSD [e.g., see Miller *et al.* (18) for a positive finding for group differences in VMPFC connectivity with different seed placement]. The DLPFC itself (similar to the VMPFC and DMPFC) is a large and heterogeneous region composed of functionally distinct subregions (59); analyzing differential patterns of rsFC across DLPFC subregions in PTSD is a goal for future research.

One limitation of the rsFC literature broadly, including the present study, concerns whether the resting-state task elicits equivalent behavior across diagnostic groups. To the extent that PTSD involves hyperattention to internal bodily signals, it is possible that the actual state sampled during resting state reflects reduced engagement in mind-wandering (and hyperengagement in attention to body sensations), which may partially account for existing rsFC findings. Addressing this possibility via pseudorandom sampling for self-report of mental activity during resting-state fMRI paradigms (60) may be an important direction for future research. An additional limitation is that, given the cross-sectional nature of the study design, it is unclear whether the present findings reflect an effect of PTSD pathology or a risk factor for developing PTSD.

In summary, in this community-based sample, adults with PTSD demonstrated increased negative DLPFC-precuneus rsFC relative to both TENC and HC subjects. This abnormality scaled with PTSD symptoms but not with early life trauma load. Further consideration of these regions as potential targets for intervention may be warranted.

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ARTICLE INFORMATION

From the Center for Depression, Anxiety and Stress Research (EAO, RHK, DAP, SLR, IMR) and McLean Imaging Center (DAP), McLean Hospital, Belmont; Department of Psychiatry (EAO, RHK, DAP, SLR, IMR), Harvard Medical School, Boston, Massachusetts; and Department of Psychology and Neuroscience (RHK), University of Colorado Boulder, Boulder, Colorado.

Address correspondence to Elizabeth A. Olson, Ph.D., Anxiety and Traumatic Stress Disorders Laboratory, McLean Hospital, Mailstop 334, 115 Mill Street, Belmont, MA 02478; E-mail: eaolson@mclean.harvard.edu.

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Regional Prefrontal rsFC in PTSD

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