Default-Mode Network Abnormalities in Pediatric Posttraumatic Stress Disorder

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Objective: Resting-state functional magnetic resonance imaging (rs-fMRI) studies of adult posttraumatic stress disorder (PTSD) have identified default-mode network (DMN) abnormalities, including reduced within-network connectivity and reduced anticorrelation between the DMN and task-positive network (TPN). However, no prior studies have specifically examined DMN connectivity in pediatric PTSD, which may differ due to neurodevelopmental factors.

Method: A total of 29 youth with PTSD and 30 nontraumatized healthy youth of comparable age and sex completed rs-fMRI. DMN properties were examined using posterior cingulate cortex (PCC) seed-based connectivity and independent component analysis (ICA).

Results: Contrary to findings in adult studies, youth with PTSD displayed increased connectivity within the DMN, including increased PCC–inferior parietal gyrus connectivity, and age-related increases in PCC–ventromedial prefrontal cortex connectivity. Strikingly, youth with PTSD also displayed greater anticorrelation between the PCC and multiple nodes within salience and attentional control networks of the TPN. ICA revealed greater anticorrelation between the entire DMN and TPN networks in youth with PTSD. Furthermore, DMN and TPN connectivity strength were positively and negatively associated, respectively, with re-experiencing symptoms of PTSD.

Conclusion: Pediatric PTSD is characterized by heightened within-DMN connectivity, which may contribute to re-experiencing symptoms of PTSD and is consistent with the role of the DMN in autobiographical memory. At the same time, greater anticorrelation between the DMN and attentional control networks may represent compensatory mechanisms aimed at suppressing trauma-related thought, a notion supported by the inverse relationship between TPN strength and re-experiencing. These findings provide new insights into large-scale network abnormalities underlying pediatric PTSD, which could serve as biomarkers of illness and treatment response.

Key words: pediatric PTSD, DMN, rs-fMRI, connectivity

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Pediatric posttraumatic stress disorder (PTSD) affects an estimated 5% of youth by the age of 18 years.[1] Pediatric PTSD has high comorbidity with other mental illnesses including anxiety disorders, depression, and attention-deficit/hyperactivity disorder (ADHD).[2] Although there is a need to advance treatments for pediatric PTSD, progress remains hampered by an incomplete understanding of underlying brain mechanisms, which may differ from those in adult PTSD because of ongoing neurodevelopment.

Resting-state functional magnetic resonance imaging (rs-fMRI) allows assessment of intrinsic (i.e., task-free) functional networks[3] and is particularly suitable in pediatric populations. Resting state analyses consistently identify 2 main networks: the default mode network (DMN), involved in self-referential processes including autobiographical memory[4-6]; and the task positive network (TPN), involved in attentional control and behavioral response via the salience, dorsal attention, and ventral attention subnetworks.[7] In healthy adults, the DMN and TPN operate in an anticorrelated fashion, indicative of functionally competing brain systems that switch during the processing of internal versus external stimuli.[8-11] DMN hyperconnectivity and reduced DMN suppression/anticorrelation have been reported in psychopathology including schizophrenia and depression, suggesting that abnormal network strength and reciprocity may underlie difficulties in disengaging from internal stimuli such as delusional thought and depressive ruminations.[11,12]

Studies in adult PTSD suggest abnormal DMN function and connectivity, including decreased within-DMN intrinsic connectivity,[13-17] both decreased[13] and increased[16] DMN-TPN intrinsic anticorrelation, and reduced DMN suppression during task.[17] Together, these findings suggest that adult PTSD is characterized by both within- and between-network abnormalities of the DMN, which may contribute to difficulties disengaging from trauma-related thought. However, no prior study has specifically examined DMN properties, including its relationship to attentional control networks, in pediatric PTSD. Thus, it remains unknown whether similar DMN abnormalities are present in pediatric as in adult PTSD, and whether the normal developmental pattern of the DMN is disrupted. Notably, DMN-TPN anticorrelation develops with age, going from positive connectivity in childhood to negative or anticorrelated connectivity by adulthood.[18]

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To address these knowledge gaps, we examined intrinsic network properties in a sample of youth with severe PTSD relative to nontraumatized healthy youth. First, we assessed DMN connectivity using seed-based connectivity of the posterior cingulate cortex (PCC), a key node of the DMN. Next, we used group independent component analysis (ICA) to examine large-scale network differences within and between the DMN and TPN. Within these analyses, we examined age-related effects cross-sectionally as an indicator of altered neurodevelopment in pediatric PTSD. We hypothesized that pediatric PTSD would be associated with disrupted within-DMN connectivity, and reduced anticorrelation between the DMN and TPN, bearing similarity to adult PTSD. Finally, we examined the relationship of DMN/TPN network properties to symptom severity using a multidimensional symptom approach, incorporating PTSD, anxiety, and depressive symptoms in this highly comorbid sample.

METHOD

Participants

Youth with PTSD and healthy youth were recruited from area mental health clinics and the community, respectively. Healthy participants were free of any history of trauma or mental illness. Exclusion criteria for all participants included IQ<70, unstable medical condition, MRI contraindication, and possibility of pregnancy. Additional exclusion criteria for the group with PTSD included active suicidality, history of psychotic disorder, bipolar disorder, obsessive-compulsive disorder, recent (past 4 weeks) substance abuse or dependence, or use of psychotropic medication (past 4 weeks; 6 weeks for fluoxetine). A total of 119 youth were screened for study inclusion. Of these, 44 were excluded at initial assessment (subthreshold for PTSD, n = 29; exclusionary diagnosis, n = 7; active substance/medication use, n = 3; no child memory of a traumatic event, n = 3; MRI contraindication, n = 1; other, n = 1). Three additional youth met study criteria but were unable to complete MRI. In all, 72 participants completed the study, including 35 youth with PTSD and 37 healthy youth. Of these, 12 were excluded based on data quality described below. The final sample includes 29 youth with PTSD (18 female and 11 male; mean age = 14.6 years) and 30 healthy youth (18 female and 12 male, mean age = 14.0 years). All participants provided written consent, or assent with caregiver consent when applicable. All procedures were approved by the University of Wisconsin Health Science Internal Review Board.

Clinical and Behavioral Assessment

Clinical assessments for this study have been previously described.[19,20] A board-certified child and adolescent psychiatrist interviewed and screened all participants, incorporating both caregiver and youth reports. Psychiatric diagnoses and trauma exposure were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS).[21] PTSD was diagnosed using *DSM-IV* criteria by combination of the K-SADS and the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA).[22,23] A PTSD diagnosis required at least 5 *DSM-IV* symptoms, including at least 1 from each symptom cluster following Cohen *et al.*[24] These criteria are slightly modified from adult criteria and were chosen to allow greater likelihood of study inclusion yet maintain a relatively high symptom severity. Furthermore, youth fulfilling 2 versus 3 symptom clusters have been reported not to differ in overall clinical impairment or distress.[25] Using these criteria, most youth in the group with PTSD (n = 24 or 83%) met full standard *DSM-IV* criteria for PTSD. Of the remaining 5 participants with PTSD, 3 met criteria for 2 symptom clusters, and 2 met criteria for 1 symptom cluster. With regard to *DSM-5* criteria, an estimated 22 participants (76%) met the full diagnosis of PTSD using conservative criteria based on extrapolation from *DSM-IV* symptoms.[26] Of the remaining 7 participants, 5 met criteria for 3 symptom clusters, and 2 met criteria for 2 symptom clusters. PTSD severity was additionally examined using the University of California, Los Angeles (UCLA) PTSD Reaction Index (PTSD-RI).[27] Because the CAPS-CA was not acquired for the first 7 participants with PTSD, PTSD-RI scores were used in lieu of CAPS-CA for secondary analyses. Here, the greater of youth and caregiver report for each item was used,[19,20] as this was most strongly correlated with CAPS scores, which represent the gold standard for PTSD assessment (r = 0.85, 0.74, and 0.60 for greater of youth/caregiver report, youth only, and caregiver only, respectively). Depressive symptoms (past 2 weeks) were quantified with the Mood and Feelings Questionnaire (MFQ).[28] Anxiety symptoms (past 3 months) were quantified with the Screen for Child Anxiety Related Emotional Disorders (SCARED).[29] MFQ and SCARED scores were calculated using the average of youth and caregiver reports. Pubertal stage was assessed by self-report using the Tanner picture-based rating scale.[30] IQ was estimated using the Full-Scale IQ-2 component of the Wechsler Abbreviated Scale of Intelligence–II.[31]

Data Acquisition

Each participant underwent 2 mock scan sessions to familiarize them to the scanning environment and reduce motion. High-resolution T1 and rs-fMRI data were acquired using a 3.0T GE Discovery MR750 scanner with an 8-channel head coil (General Electric Medical Systems, Waukesha, WI). High-resolution T1 images were acquired using a BRAVO pulse sequence (with axial orientation, TE =3.18 milliseconds, TR = 8.16 milliseconds, TI = 450 milliseconds, voxel size = 1 × 1 × 1 mm^3, 156 slices, flip angle = 12 degrees, field of view [FOV] = 25.6 cm, and matrix size = 256 × 256). rs-fMRI was acquired using an echo-planar imaging (EPI) pulse sequence (with sagittal orientation, TE = 22 milliseconds, TR = 2150 milliseconds, flip angle = 79 degrees, slice thickness = 3 mm, gap = 0.5 mm, 41 slices, FOV = 224 mm, and matrix size = 64 × 64, number of volumes = 147 [5 minutes 16 seconds]). For rs-fMRI, participants were instructed to remain still with their eyes fixed on a cross.

rs-fMRI Preprocessing

Preprocessing was carried out using AFNI.[32] Figure S1, available online, shows the preprocessing pipeline used for each research participant. The steps were: deletion of the first 3 volumes; despiking of rs-fMRI data; slice-timing correction; co-registration of T1 and EPI images; realignment of EPI volumes and normalization to Montreal Neurological Institute (MNI) template in a single step (final resolution 2 mm isotropic for visualization with template underlay); spatial smoothing (6 mm full width at half maximum [FWHM]); anatomy segmentation; and nuisance regression (eroded white matter and cerebrospinal fluid masks, 6 motion parameters and their derivatives) and temporal filtering (0.01–0.1Hz) along with motion censoring in a single step. Volumes were motion censored using a threshold of 0.25 mm based on framewise displacement calculated using the Euclidean norm. Participants having 37 or more volumes (25%) flagged by the censoring algorithm were excluded from the study, resulting in 12 exclusions (6 PTSD and 7 healthy participants). The average motion in all directions was calculated and compared across groups; no difference in motion was observed (Table S1, available online).

Connectivity Analysis: Seed-Based

DMN connectivity was calculated using a 4-mm-radius sphere located in the PCC (MNI coordinates [RAI]: 2, 52, 26). Individual connectivity maps were converted from r to Z using a Fisher-Z transform. Group differences in connectivity were examined using an analysis of covariance (ANCOVA) in AFNI (3dttest++), with covariates including age, sex, and their interaction with group. Multiple comparison correction was performed using Monte Carlo simulation, which incorporates the estimated data smoothness to establish the likelihood of false-positive results of different cluster sizes.[33] The cluster threshold was 152 voxels at a voxelwise threshold of $p = .005$, resulting in a corrected $\alpha = 0.05$.

Connectivity Analysis: Independent Component Analysis

Resting-state networks were identified using a spatial group independent component analysis, implemented in GIFT.[34] Data input to the ICA were first preprocessed by correcting for participant motion using rigid-body realignment of EPI volumes, correction for slice timing, alignment of EPI data to the T1-weighted structural image, transformation (linear affine and nonlinear) to MNI space, and spatial smoothing with a Gaussian kernel (FWHM 6 mm). Within GIFT, dimensionality was first reduced using principal components analysis (PCA) at the individual level. A total of 40 independent components were estimated at the group level using the Infomax algorithm.[35] Group data were then back-reconstructed to individual participants. ICA maps were thresholded using the default setting in GIFT.

The component representing the DMN (consisting of posterior cingulate/precuneus, lateral parietal cortex, and medial prefrontal cortex) and a component representing the TPN (dorsolateral prefrontal cortex, frontoinsular cortex, dorsal anterior cingulate/presupplementary motor area, intraparietal sulcus) were visually identified from the group results. Between-network functional connectivity was estimated by computing the correlation between these 2 ICA component time series for each participant. ANCOVA was then conducted in AFNI (3dttest++) to examine group differences in average network and between-network connectivity covarying for age and sex. Because of the targeted, exploratory nature of the 3 ICA analyses, additional adjustment for multiple comparisons was not applied.

Post Hoc Analyses

Post hoc analyses were conducted on extracted cluster averages in *R* (R Core Team, 2014) to examine the following: potential confounds in group differences; relationships to PTSD, depression, and anxiety symptoms; and relationship to trauma exposure within the group with PTSD, covarying for age and sex. Given high rates of comorbid affective and anxiety disorders in our sample, we used a multidimensional symptom approach to examine the relationship between symptom measures and brain findings within the group with PTSD. Specifically, we performed data reduction using PCA of PTSD,

TABLE 1 Participant Characteristics

Characteristic	Healthy	PTSD
Sample size	30	29
Sex	18 F, 12 M	18 F, 11 M
Age, y (SD)	14.0 (2.3)	14.6 (2.6)
IQ (SD)	109 (12)	102 (12)
Tanner stage (SD)	3.3 (1.3)	3.4 (1.3)
Handedness	27 R, 3A	23 R, 5 L, 1 A
PTSD duration, mo (SD)	—	46 (38)
PTSD-RI	—	47 (14)
CAPS-CA	—	70 (21)
MFQ	3 (2)	30 (21)
SCARED	7 (5)	38 (23)
Index trauma [n]	—	Sexual abuse [13]
		Accident [6]
		Traumatic death of loved one [7]
		Witness of domestic violence [4]
		Physical abuse [1]
Comorbid diagnosis [n]	—	MDD [17]
		ADHD [7]
		GAD [8]
		Social anxiety disorder [4]
		Separation anxiety disorder [4]
		Depressive disorder NOS [3]
Past psychiatric medication [n]	—	SSRI/SNRI [8]
		Stimulant [8]
		α_2 Agonist [2]

Note: Groups did not significantly differ in age, IQ, or Tanner stage. The Clinician-Administered PTSD (posttraumatic stress disorder) Scale for Children and Adolescents (CAPS-CA) was not obtained for the first 7 participants with PTSD. A = Ambidextrous; ADHD = attention-deficit/hyperactivity disorder; F = females; GAD = generalized anxiety disorder; L = left-handed; M = males; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; NOS = not otherwise specified; PTSD-RI = PTSD Reaction Index; R = right-handed; SCARED = Screen for Child Anxiety Related Emotional Disorders; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

depressive, and anxiety symptoms from the PTSD-RI, MFQ, and SCARED in a slightly expanded sample of youth with PTSD (n = 31) including all participants in the current study. This approach allows for avoidance of collinearity in symptom analysis and minimization of the number of statistical tests, although generalizability to other populations may be limited. For this reason, we also report standard symptom relationships (see Supplement 1, available online). Items with low correlation coefficients in all components (<0.4) and/or low measures of sampling adequacy (<0.5) were removed. Principal component loadings for each item were rotated using the Varimax method with Kaiser normalization. Component inclusion was based on an eigenvalue of 1 or greater.

Five components were extracted from the final iteration of PCA, explaining 74.8% of the total variance in symptom measures. Based on the items loading to each component, the 5 symptom domains included (with percent of total variance explained): social aversion (20.7%), hopelessness (18.0%), negative affect (14.1%), hyperarousal (12.0%), and re-experiencing (10.0%) (Table S2, available online). These 5 components reached significance for Bartlett's test of sphericity ($p < .0001$) and had a Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy = 0.609. The specific PTSD-RI, MFQ, and SCARED items loading into each component can be found in Supplement 1, available online. Component scores for each participant with PTSD were calculated and used in post hoc analyses.

RESULTS

Participant Characteristics

A summary of participant characteristics is shown in Table 1. The healthy and PTSD groups did not differ in age, IQ, female-to-male ratio, or pubertal stage. For the group with PTSD, the average PTSD-RI score was 47, which is indicative of severe PTSD. The most common index trauma was sexual abuse, followed by accident, traumatic death of a loved one, and witnessing domestic violence. Of the 29 participants with PTSD, 26 had comorbid psychiatric illness, most commonly depressive disorders (n = 20).

DMN Connectivity Abnormalities in Pediatric PTSD: Seed-Based Analysis

Using the PCC seed, the DMN was consistently present in participants from both groups (Figure 1). A summary of seed-based connectivity findings can be found in Table 2. Within the DMN, youth with PTSD showed increased connectivity between the PCC and left inferior parietal gyrus (IPG, Brodmann area [BA] 40). Youth with PTSD also showed reduced (more anticorrelated) connectivity between the PCC and multiple regions associated with the task-positive network (Figure 1). These regions included the right intraparietal sulcus (IPS, BA 40), right inferior frontal gyrus extending into the insular cortex (IFG, BA 6/22), and dorsal anterior cingulate cortex/presupplementary motor area (dACC/pre-SMA, BA 32/24). Similar effects were observed for the left IPS and IFG at lower cluster extent thresholds (Figure S2, available online). Finally, a group-by-age interaction was present for connectivity within the DMN. Specifically, PCC connectivity to the ventromedial prefrontal cortex (vmPFC, BA 11) decreased with age in healthy youth but increased with age in youth with PTSD (Figure S3, available online).

DMN Connectivity Abnormalities in Pediatric PTSD: Independent Component Analysis

ICA results are summarized in Figure 2. Components for the DMN and TPN were identified across the entire sample, showing similarity to seed-based connectivity patterns.

FIGURE 1 Default-mode network (DMN) connectivity differences between youth with posttraumatic stress disorder (PTSD) and healthy youth using a posterior cingulate cortex (PCC) seed-based connectivity analysis. Note: Respective group maps are shown as well as group connectivity differences, adjusting for age and sex. Youth with PTSD showed increased connectivity within the DMN (PCC left inferior parietal gyrus [IPG]), but also greater anticorrelation between the PCC and multiple nodes of attentional control networks (right inferior frontal gyrus [IFG]/insula, right intraparietal sulcus [IPS], dorsal anterior cingulate cortex [dACC]/presupplementary motor area [SMA]). Maps are shown at a voxelwise $p = .005$ and minimum cluster extent of 152 voxels. Hyphen represents a subtraction operation; equal sign represents the results of the subtraction operation.

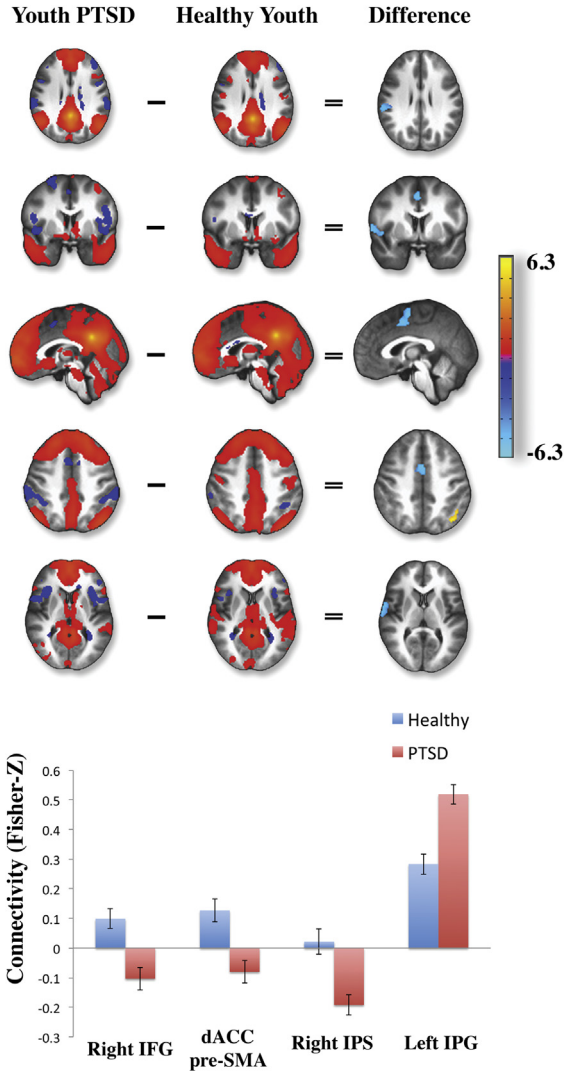


TABLE 2 Significant Clusters Observed in the Posterior Cingulate Cortex (PCC) Seed-Based Connectivity Analysis

Contrast	Region	BA	Network	x	y	z	Peak *t*	No. of Voxels
Healthy > PTSD youth	Right IFG	6, 22	TPN	−66	6	6	−4.55	300
	dACC/pre-SMA	6, 24	TPN	−2	6	60	−4.32	282
	Right IPS	40	TPN	−60	26	32	−3.76	200
PTSD > healthy youth	Left IPG	40	DMN	46	56	54	4.55	188
Group × age:	MFG	11	DMN	6	−62	−14	4.67	163
PTSD > healthy youth	Cerebellum	—	—	−26	70	−30	3.92	205

Note: The peak coordinates are in Montreal Neurological Institute (MNI) space (RAI orientation). Peak t statistics are derived from the contrast posttraumatic stress disorder (PTSD)—Healthy. BA = Brodmann area; dACC = dorsal anterior cingulate cortex; DMN = default-mode network; IPG = inferior parietal gyrus; IPS = inferior parietal sulcus; Pre-SMA = presupplementary motor area; TPN = task-positive network; vmPFC = ventromedial prefrontal cortex.

Analysis of extracted, average network connectivity strength for each component revealed no overall differences in DMN or TPN strength between healthy youth and those with PTSD. However, consistent with seed-based findings, youth with PTSD displayed reduced (more anticorrelated) connectivity between the DMN and TPN components compared to healthy youth (–0.29 and –0.12, respectively, $t_{53} = -2.25$, $p = .029$).

To facilitate comparison between the seed-based and ICA connectivity findings, the overlap was examined between seed-based clusters and the DMN and TPN component maps derived from ICA. Here, the IPS, IFG, and dACC clusters derived from the seed-based analysis overlapped closely with the TPN component (91%, 93%, and 99.6%, respectively) but showed no overlap with the DMN component. Conversely, the IPG and vmPFC clusters overlapped the DMN component (23.9% for both) but showed no overlap with the TPN component.

Post Hoc Analyses

To examine potential confounds in group main effects, post hoc analyses were conducted on average PCC and ICA connectivity, adjusting for age, sex, IQ, and past exposure (in months) to α-agonists, selective serotonin reuptake inhibitors (SSRIs)/serotonin–norepinephrine reuptake inhibitors (SNRIs), and stimulants. All group main effects remained significant within these models ($p < .05$). In addition, age-related increases in PCC-vmPFC connectivity in the group with PTSD remained significant with adjustment for time elapsed since trauma ($\beta = 0.261$, $t_{21} = 3.186$, $p = .004$).

Next, the relationship between connectivity measures and symptom dimensions was examined within the group with PTSD, adjusting for age and sex. For the PCC seed analysis, PCC–IPG connectivity was positively associated with re-experiencing symptoms ($\beta = 0.433$, $t_{21} = 2.229$, $p = .037$; Figure 3). In addition, PCC–cerebellum connectivity was negatively associated with social aversion symptoms ($\beta = -0.460$, $t_{21} = -3.425$, $p = .002$). For the ICA analysis, average TPN connectivity strength was negatively associated with re-experiencing symptoms ($\beta = -0.445$, $t_{21} = -2.418$, $p = .025$; Figure 3). Connectivity between the DMN and TPN was positively associated (trend level) with symptoms of hopelessness ($\beta = 0.386$, $t_{21} = 2.032$, $p = .055$). No significant relationship was observed between connectivity measures and negative affect or hyperarousal symptom dimensions.

Finally, the relationship between connectivity measures and trauma exposure measures (time elapsed since index trauma, index trauma type, number of trauma types endorsed) was examined within the group with PTSD, adjusting for age and sex. PCC–IPG connectivity was significantly associated with index trauma type ($F_{7,21} = 3.751$, $p = .008$), such that youth with interpersonal index traumas had greater connectivity relative to accident index trauma ($t_{21} = -3.211$, $p = .004$). No significant relationships were observed with time elapsed since index trauma or trauma load.

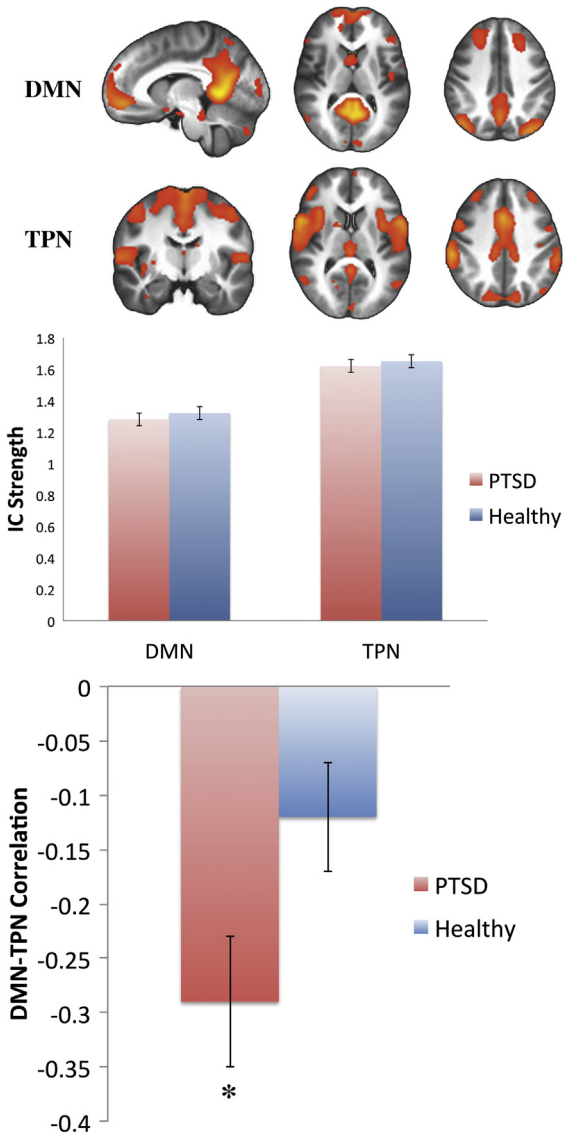
DISCUSSION

To our knowledge, this is the first reported study to examine DMN properties, including their relationship with task-positive networks, in pediatric PTSD. Contrary to expectations and reports in adult PTSD, our findings revealed greater connectivity within the DMN in pediatric PTSD. Greater within-DMN connectivity (PCC to IPG connectivity) was further associated with re-experiencing symptoms, suggesting that a network known to underlie self-referential processing may also contribute to intrusive trauma-related thought in youth. At the same time, youth with PTSD showed abnormal anticorrelation between the DMN and task-positive attentional control networks, a pattern bearing similarity to healthy adults. TPN connectivity strength, in turn, was inversely correlated with re-experiencing symptoms, directly implicating attentional control networks in the suppression of trauma-related thought in youth. Together, these novel findings suggest striking abnormalities in brain networks underlying self-referential thought and attentional control in pediatric PTSD, which may offer important targets for intervention in affected youth.

Surprisingly, we found no evidence for weaker connectivity within the DMN in pediatric PTSD, which stands in stark contrast to studies of adult PTSD.[13-17] On the contrary, our findings revealed increased within-DMN connectivity in pediatric PTSD, specifically between the PCC and IPG. Furthermore, youth with PTSD showed age-related increases in connectivity between the PCC and vmPFC, suggesting that within-DMN connectivity strength may

become even more pronounced over the course of development in trauma-exposed youth with PTSD. In addition to these group differences, post hoc analyses revealed that PCC–IPG connectivity was positively associated with re-experiencing symptoms but was unrelated to anxiety, depressive, or other PTSD symptoms. This is particularly intriguing, given the role of these regions, and the DMN more generally, in autobiographical memory retrieval as well as envisioning future scenarios.[6] Thus, increased connectivity within the DMN may underlie, in part, the persistence of trauma-related memory and worry in affected youth.

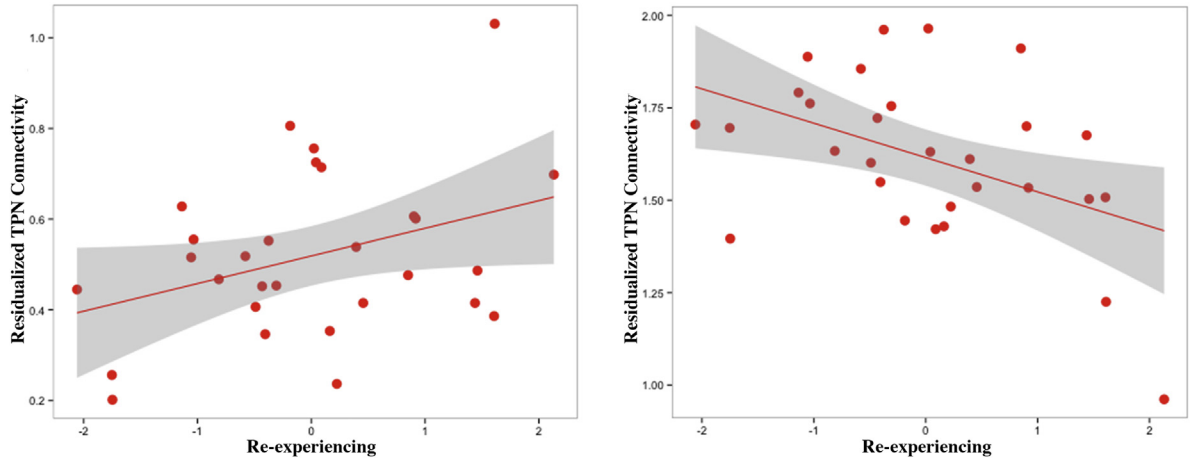
FIGURE 2 Independent component analysis of default-mode network (DMN) and task-positive network (TPN) connectivity in youth with posttraumatic stress disorder (PTSD) and healthy youth. Note: PTSD and healthy youth did not differ in overall DMN and TPN connectivity strength but showed reduced overall connectivity between the DMN and TPN. DMN and TPN component maps are shown in the top panel. In the middle panel, bar graphs show the average connectivity strength for each group, and each of the 2 components. The bottom panel shows the correlation between the DMN and TPN components for each group. Error bars represent standard error of the mean. IC = independent component. *$p < .05$.



At present, it remains unclear why these current findings differ from adult PTSD, where studies have consistently shown reduced within-DMN connectivity.[13-17] One possibility is that trauma exposure during childhood may have different effects on the DMN compared to adult trauma. However, reduced DMN connectivity has been reported even in adults with PTSD due to childhood trauma.[14] Another alternative is that neural representations of re-experiencing are different between youth and adults with PTSD. However, prior studies of adult PTSD have not shown any clear relationship between reduced DMN connectivity or PTSD severity. A related possibility, then, is that reduced within-DMN connectivity in adult PTSD actually represents a delayed, compensatory decrease in DMN connectivity that may serve to counteract re-experiencing symptoms. These hypotheses would clearly require further testing in future studies, including longitudinal examination of youth with PTSD into adulthood. Although the current DMN findings do differ from adult PTSD, it is worth noting that increased within-DMN connectivity has been consistently reported in both youth and adults with major depressive disorder (MDD),[12] discussed further below.

In addition to within-DMN connectivity differences, our study revealed prominent abnormalities in connectivity between the DMN and task-positive networks in pediatric PTSD. Specifically, in the seed-based analysis, youth with PTSD showed abnormal anticorrelation between the PCC and nodes of the salience network (dACC/SMA), dorsal attention network (IPS), and ventral attention network (IFG/insula). In adults, these networks are normally anticorrelated with the DMN at rest.[8-10] However, this pattern may be different in children, in whom DMN-TPN connectivity is either positive or only slightly negative,[18] as observed in our healthy youth. The salience, ventral attention, and dorsal attention subnetworks of the TPN subserve stimulus detection, attentional redirection, and attentional maintenance, respectively, for external tasks.[7] Crucial to the functioning of these networks in attentional control is the suppression of the DMN (and vice versa for self-referential thought). As such, anticorrelation between the DMN and TPN appears to represent functional competition between these networks. Notably, our findings revealed that TPN connectivity strength was inversely related to re-experiencing symptoms, suggesting that the magnitude of coupling in attentional networks may confer a greater ability to suppress trauma-related thought. In light of this, greater DMN-TPN anticorrelation in pediatric PTSD may represent a compensatory mechanism to suppress unwanted thought, perhaps reflecting early maturation of these networks toward adult connectivity patterns. Although DMN-TPN anticorrelation was not directly associated with re-experiencing, it was associated

FIGURE 3 Re-experiencing symptoms are related to default-mode network (DMN) and task-positive network (TPN) connectivity strength in youth with posttraumatic stress disorder (PTSD). Note: Left panel: within the DMN, connectivity between the posterior cingulate cortex (PCC) and inferior parietal gyrus (IPG; derived from the seed-based analysis) predicts greater re-experiencing symptom severity. Right panel: TPN connectivity strength (derived from independent component analysis [ICA]) predicts lower re-experiencing symptom severity. Scatterplot values are adjusted for age, sex, and other symptom dimensions.



with symptoms of hopelessness, suggesting that anti-correlation of these networks could underlie perceptions of symptom controllability when attempting to engage in outward-focused tasks.

Given the high comorbidity of depressive disorders in our sample, it is worth noting that MDD has also been associated with DMN abnormalities. A recent meta-analysis showed that adult MDD is characterized by increased within-DMN connectivity, but that DMN-TPN connectivity may be either increased or decreased depending on the TPN subnetwork examined.[12] Although less is known about DMN properties in pediatric depression, studies to date consistently implicate increased anterior DMN connectivity, which is further associated with symptom severity and rumination.[36] Surprisingly, we found relatively few associations with depressive symptoms and DMN measures in our sample, with the possible exception of DMN-TPN anti-correlation and hopelessness noted above. On the other hand, the use of a PCC (and not anterior DMN) seed may have precluded more depression-specific findings. In either case, our findings suggest that pediatric PTSD may share some commonality with depression in terms of hyper-connectivity within the DMN, which may contribute to the pathological persistence of self-referential thought in both disorders, namely depressive rumination and traumatic re-experiencing. Clearly, future studies are needed to explore DMN abnormalities both common and specific to depression and PTSD, and whether symptom improvement is associated with normalization of DMN connectivity.

Although our study presents novel findings of abnormal intrinsic network connectivity in pediatric PTSD, it is not without limitations. First, this study did not include trauma-exposed healthy youth, which will be important in fully teasing apart the effects of trauma versus PTSD. However, our post hoc analyses suggest differential relationships of symptom and trauma exposure measures with network connectivity, which has the benefit of examining these variables within participants. Second, group differences are based on cross-sectional data, and we are not able to determine whether network abnormalities are premorbid traits, acquired following trauma exposure, or with the development of PTSD or its comorbidities. Future studies using a longitudinal design will be needed to examine these possibilities. Third, although our symptom dimension analyses suggest specificity of effects to re-experiencing symptoms of PTSD, future work examining resting state networks across multiple diagnostic groups (e.g., depression only, PTSD only) will be needed to fully explore diagnostic specificity versus commonality. Fourth, although the exploratory ICA analysis confirms the seed-based results, these 2 analyses may not be completely independent, given that DMN and TPN components were identified visually with a priori knowledge of the seed-based results. Finally, the PCA symptom dimensions were generated from a relatively small sample for the purposes of data reduction and may not generalize to other study populations.

In summary, the present findings revealed abnormal default mode network properties in pediatric PTSD that appear to differ markedly from those in adult PTSD. Namely, youth with PTSD showed increased connectivity within the DMN, which may directly contribute to re-experiencing of traumatic memory and is consistent with the role of the DMN in autobiographical memory and rumination. On the other hand, youth with PTSD showed greater anticorrelation between the default mode and attentional control networks, which may reflect a compensatory mechanism to reduce trauma-related thought through opposition of the DMN. These intrinsic network patterns point to potential neural targets for therapeutic interventions that aim to regulate traumatic

re-experiencing in youth. In particular, future studies might examine whether psychotherapy such as trauma-focused cognitive-behavioral therapy is capable of reducing connectivity within the default mode network, and whether such therapies may also further strengthen attentional control networks to reduce symptoms of PTSD in affected youth. &

CG Clinical Guidance

- Youth with PTSD show abnormal functional connectivity of the brain's default mode network (DMN), which is involved in self-related thought and autobiographical memory.
- Youth with PTSD have abnormally increased connectivity within the DMN, which may contribute to re-experiencing of traumatic memory.
- Youth with PTSD also have greater opposing connectivity between the DMN and attentional control networks, which may to help them to "switch out" of the DMN and suppress traumatic memory.
- These default mode network abnormalities are quite different from those in adult PTSD and highlight the importance of studying brain networks in PTSD developmentally.

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REFERENCES

1. Merikangas KR, He JP, Burstein M, *et al*. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010;49:980-989.
2. Famularo R, Fenton T, Kinscherff R, Augustyn M. Psychiatric comorbidity in childhood post traumatic stress disorder. Child Abuse Neglect. 1996;20:953-961.
3. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995;34:537-541.
4. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci. 2001;98:676-682.
5. Anticevic A, Cole MW, Murray JD, Corlett PR, Wang XJ, Krystal JH. The role of default network deactivation in cognition and disease. Trends Cogn Sci. 2012;16:584-592.
6. Spreng RN, Grady CL. Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. J Cogn Neurosci. 2010;22:1112-1123.
7. Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. Neuron. 2008;58:306-324.
8. Chai XJ, Castanon AN, Ongur D, Whitfield-Gabrieli S. Anticorrelations in resting state networks without global signal regression. Neuroimage. 2012;59:1420-1428.
9. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci. 2005;102:9673-9678.
10. Fox MD, Zhang D, Snyder AZ, Raichle ME. The global signal and observed anticorrelated resting state brain networks. J Neurophysiol. 2009;101:3270-3283.
11. Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. Ann Rev Clin Psychol. 2012;8:49-76.
12. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatry. 2015;72:603-611.
13. Sripada RK, King AP, Welsh RC, *et al*. Neural dysregulation in posttraumatic stress disorder: evidence for disrupted equilibrium between salience and default mode brain networks. Psychosom Med. 2012;74:904-911.
14. Bluhm RL, Williamson PC, Osuch AO, *et al*. Alterations in default mode network connectivity in posttraumatic stress disorder related to early-life trauma. J Psychiatry Neurosci. 2009;34:187-194.
15. Shang J, Lui S, Meng Y, *et al*. Alterations in low-level perceptual networks related to clinical severity in PTSD after an earthquake: a resting-state fMRI study. PLoS One. 2014;9:e96834.
16. Zhang Y, Liu F, Chen H, *et al*. Intranetwork and internetwork functional connectivity alterations in post-traumatic stress disorder. J Affect Disord. 2015;187:114-121.
17. Chen AC, Etkin A. Hippocampal network connectivity and activation differentiates post-traumatic stress disorder from generalized anxiety disorder. Neuropsychopharmacology. 2013;38:1889-1898.
18. Chai XJ, Ofen N, Gabrieli JD, Whitfield-Gabrieli S. Selective development of anticorrelated networks in the intrinsic functional organization of the human brain. J Cogn Neurosci. 2014;26:501-513.
19. Keding TJ, Herringa RJ. Abnormal structure of fear circuitry in pediatric post-traumatic stress disorder. Neuropsychopharmacology. 2015;40:537-545.
20. Wolf RC, Herringa RJ. Prefrontal-amygdala dysregulation to threat in pediatric posttraumatic stress disorder. Neuropsychopharmacology. 2016;41:822-831.
21. Kaufman J, Birmaher B, Brent D, *et al*. Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997;36:980-988.
22. Nader KO, Newman E, Weathers FW, Kaloupek DG, Kriegler JA, Blake DD. Clinician-Administered PTSD Scale for Children and Adolescents for DSM-IV. White River Junction, VT: National Center for PTSD; 1998.

23. Weathers FW, Keane TM, Davidson JRT. Clinician-administered PTSD scale: a review of the first ten years of research. Depress Anxiety. 2001;13: 132-156.
24. Cohen JA, Mannarino AP, Iyengar S. Community treatment of post-traumatic stress disorder for children exposed to intimate partner violence. Arch Pediatr Adolesc Med. 2011;165:16-21.
25. Carrion VG, Weems CF, Ray RR, Reiss AL. Toward an empirical definition of pediatric PTSD: the phenomenology of PTSD symptoms in youth. J Am Acad Child Adolesc Psychiatry. 2002;41:166-173.
26. Rosellini AJ, Heeringa SG, Stein MB, *et al*. Lifetime prevalence of DSM-IV mental disorders among new soldiers in the U.S. Army: results from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). Depress Anxiety. 2015;32:13-24.
27. Steinberg AM, Brymer MJ, Decker KB, Pynoos RS. The University of California at Los Angeles Post-traumatic Stress Disorder Reaction Index. Curr Psychiatry Rep. 2004;6:96-100.
28. Costello EJ, Angold AA. Scales to assess child and adolescent depression: checklists, screens, and nets. J Am Acad Child Adolesc Psychiatry. 1988; 27:726-737.
29. Birmaher B, Khetarpal S, Brent D, *et al*. The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. J Am Acad Child Adolesc Psychiatry. 1997;36:545.
30. Morris NM, Udry JR. Validation of a self-administered instrument to assess stage of adolescent development. J Youth Adolesc. 1980;9:271.
31. Wechsler D. Wechsler Abbreviated Scale of Intelligence–Second Edition Manual. Bloomington, MN: Pearson; 2011.
32. Cox R. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res. 1996;29: 162-173.
33. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn Reson Med. 1995;33:636-647.
34. Allen EA, Erhardt EB, Damaraju E, *et al*. A baseline for the multivariate comparison of resting-state networks. Front Syst Neurosci. 2011;5:2.
35. Bell AJ, Sejnowski TJ. An information-maximization approach to blind separation and blind deconvolution. Neural Comput. 1995;7: 1129-1159.
36. Kerestes R, Davey CG, Stephanou K, Whittle S, Harrison BJ. Functional brain imaging studies of youth depression: a systematic review. Neuroimage Clin. 2014;4:209-231.