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NeuroImage: Clinical

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Altered resting-state functional connectivity in adolescents is associated with PTSD symptoms and trauma exposure

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ARTICLE INFO

Keywords:

Posttraumatic stress disorder
Trauma
Adolescents
Resting-state
Functional connectivity
fMRI

ABSTRACT

Alterations in resting-state functional connectivity (rsFC) have been demonstrated in Posttraumatic Stress Disorder (PTSD). However, such reports have primarily focused on adult participants, whereas findings in adolescents with PTSD are mixed and not entirely consistent with the adult literature. Here, we examined rsFC in a non-treatment seeking adolescent sample with posttraumatic stress symptoms (PTSS; $n = 59$) relative to asymptomatic controls ($n = 226$). We also examined differences between trauma-exposed and non-exposed control subgroups (TEC $n = 73$ and Non-TEC $n = 153$) to examine alterations associated with more general trauma exposure. Finally, we compared the PTSS and TEC groups, to confirm that the reported alterations in PTSS were not driven by trauma exposure. Using a seed-based approach, we examined connectivity of default-mode (DMN) and salience (SN) networks, where alterations have been previously reported. Results suggest that PTSS are associated with less within-DMN connectivity and greater SN-DMN connectivity, as well as altered connectivity with attention regions. Trauma exposure is associated with greater within-SN connectivity. Additionally, we report findings from exploratory connectome-based analysis, which demonstrate a number of topological alterations within DMN in the PTSS group. Overall, our findings replicate prior reports of altered rsFC in PTSD and extend them to non-treatment seeking, trauma-exposed adolescents, who did or did not report PTSS. They specifically highlight SN-DMN desegregation, lower within-DMN and greater within-SN connectivity, as well as altered connectivity with attention regions, in trauma-exposed adolescents. Future research is required to confirm that adolescents with diagnosed PTSD have similar/exacerbated connectivity patterns.

1. Introduction

Posttraumatic Stress Disorder (PTSD) is a highly debilitating psychiatric condition with a lifetime prevalence of around 8%, with higher rates associated with multiple traumatic events (Kessler, 2000; Tamburrino et al., 2015; Thompson et al., 2006). PTSD is characterized by four clusters of symptoms, including intrusive trauma-related memories, avoidance of trauma reminders, physiological arousal, and

negative mood and cognition (American Psychiatric Association, 2013). Early life exposure to trauma has been linked to development of adolescent PTSD at rates up to 35% (de Vries et al., 1999; Walker et al., 2004), taking an immense negative toll on development and impacting learning and memory functions (Samuelson et al., 2010). Given the effects adolescent PTSD can have on development, a better understanding of mechanisms underlying adolescent PTSD is imperative.

Numerous neuroimaging studies over the past two decades have

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<https://doi.org/10.1016/j.nicl.2020.102215>

Received 8 August 2019; Received in revised form 13 February 2020; Accepted 16 February 2020

Available online 19 February 2020

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aimed to identify neural mechanisms underlying PTSD development and accompanying cognitive and emotion processing deficits, primarily in adult populations. Accumulating evidence suggests that people with PTSD have alterations in connectivity within and between large-scale intrinsic connectivity networks (ICNs). Notably, resting-state functional connectivity (rsFC) studies in PTSD often report abnormalities in Default-Mode Network (DMN), which is linked to self-referential processing and mind wandering, with key nodes in posterior cingulate cortex (PCC), ventromedial prefrontal cortex (vmPFC), and hippocampus; and Salience Network (SN), which is linked to salience/threat detection, with key nodes in insula/operculum, dACC, and amygdala (Liberzon and Abelson, 2016). Specifically, seed-based connectivity studies suggest that participants with PTSD have reduced connectivity within DMN, increased connectivity within SN, and desegregation (i.e., greater connectivity) between DMN and SN compared to healthy controls (Sripada et al., 2012b; Tursich et al., 2015). Increased connectivity between DMN and SN with regions involved in attention control and orienting have also been reported in PTSD patients (Block et al., 2017; Block and Liberzon, 2016).

In addition to using a specific *a priori* seed (e.g., amygdala) to investigate connectivity between the seed and other regions (either across whole brain or other previously defined regions), rsFC patterns can be studied using connectome-wide, data-driven approaches. Such approaches aim to address challenges inherent to studies of *a priori* regions, i.e., failure to adequately reflect the complex functional organization of the brain. For instance, graph-theory analysis allows the examination of whole-brain functional architecture, including functional segregation, functional integration, and equilibrium between segregation and integration (Rubinov and Sporns, 2010; Wang et al., 2011). Studies utilizing graph theory report that PTSD are associated with alterations in small-worldness (connection length between clusters within the network), with reports of both decreased (Du et al., 2015; Jung et al., 2016) and increased (Zhang et al., 2017) small-world topology. Additionally, both decreased (Du et al., 2015; Jung et al., 2016) and increased (Lei et al., 2015) global clustering (amount of interconnections between neighboring regions) and altered characteristic path length (length of shortest connections between various regions) (Du et al., 2015; Lei et al., 2015; Long et al., 2013) have been observed in PTSD. This approach can also interrogate distinct topological characteristics of specific ICNs. For instance, Akiki et al. (2018) reported that PTSD symptom severity was associated with less DMN strength (degree of connections between regions) and greater DMN modularity (amount of sparsely interconnected modules, each containing densely intraconnected nodes), while Lei et al. (2015) reported that both DMN and SN have greater centrality in PTSD (amount of nodes with high number of paths passing through them). In addition to graph theory, connectome-based predictive modeling (CPM) has been developed to test whether individual's symptoms or diagnosis can be predicted based on the organization of nodes and edges in their connectome (Shen et al., 2017). To date, no studies have reported CPM results in a PTSD sample. Analyzing datasets using multiple analytic methods, including both seed-based and connectome-based approaches, can help us further establish and replicate patterns of functional connectivity associated with PTSD symptoms (PTSS).

Importantly, reports of rsFC in PTSD using either seed-based or connectome-based analysis have primarily focused on adults, the majority of whom were treatment seeking. Few studies have examined patterns of rsFC in adolescents with PTSD, and findings are mixed. Some reports are consistent with the adult PTSD literature, suggesting that PTSS in adolescents are associated with greater connectivity within SN regions (Nooner et al., 2013), decreased connectivity within DMN regions (Viard et al., 2019), and greater connectivity between DMN and regions of the Dorsal Attention Network (DAN) involved in attentional control (Cisler et al., 2013). Others, in contrast to the adult PTSD literature, report that adolescents with PTSD have greater connectivity within DMN (Patriat et al., 2016), higher segregation (i.e., less

connectivity) between DMN and SN (Cisler et al., 2013; Wolf and Herringa, 2016), and between DMN and regions of the Ventral Attention Network (VAN), involved in alerting and orienting attention (Patriat et al., 2016). In addition, in adolescents with PTSD, there was less local and global efficiency and nodal centrality in DMN (Suo et al., 2017), greater nodal centrality in DMN, increased clustering coefficient, and increased path length (Suo et al., 2015). Overall, findings in adolescents with PTSD from rsFC studies are mixed and not entirely consistent with the findings reported in adult PTSD samples. Further examination of rsFC patterns in adolescents with PTSS is needed for a comprehensive understanding of neural mechanisms underlying PTSS across development.

To address this gap in the literature, the current study aimed to utilize a series of both seed-based and connectome-wide approaches to examine rsFC in adolescents with PTSS compared to asymptomatic controls. To isolate differences in brain connectivity associated with trauma exposure and with PTSS specifically, we ran two additional comparisons. To examine differences associated with trauma exposure, we compared the trauma-exposed (TEC) and non-trauma-exposed (Non-TEC) subgroups. To examine differences associated with PTSS while controlling for trauma exposure, we compared the PTSS and TEC groups. We hypothesized that participants with PTSS would have greater within-SN connectivity, previously reported in both the adult and adolescent literature, and which might underlie hypervigilant behavioral manifestations (Nooner et al., 2013; Sripada et al., 2012b; Tursich et al., 2015). While we also hypothesized abnormalities in within-DMN and SN-DMN connectivities, due to inconsistent adult and adolescent literature (e.g., lower within-DMN connectivity and greater SN-DMN desegregation in PTSD reported by (Sripada et al., 2012b; Tursich et al., 2015; Viard et al., 2019) vs. opposite patterns reported by (Cisler et al., 2013; Patriat et al., 2016; Wolf and Herringa, 2016)), we did not make predictions about the exact nature of such abnormalities. Based on recent reports, we also explored differences in connectivities between DMN, SN and attention regions (Block et al., 2017; Block and Liberzon, 2016). Due to the limited evidence of such alterations in adult PTSD, and lack of investigations in adolescent PTSD, no specific hypotheses were made. Finally, to supplement and confirm our seed-based analyses, we examined whole-brain functional architecture and topological properties of networks, using data-driven graph-theory analysis and CPM. We expected to see PTSS-related differences in DMN and SN topological properties.

2. Methods

All procedures for recruitment, assessment and neuroimaging have been detailed in previous publications from the Philadelphia Neurodevelopmental Cohort (PNC; Satterthwaite et al., 2016, 2014) and are briefly summarized below. The institutional review boards of the University of Pennsylvania and the Children's Hospital of Philadelphia approved all study procedures and informed consent was obtained from all the participants.

2.1. Participants

Participants were obtained from the PNC, a large-scale NIMH-funded initiative to examine, among others, the association between brain activation and psychiatric illness in adolescents (Satterthwaite et al., 2016). Out of a pool of 1445 participants who underwent magnetic resonance imaging (MRI) scanning, a total of 376 participants with posttraumatic stress symptoms (PTSS), trauma-exposed controls (TECs) and non-trauma-exposed controls (Non-TECs) were identified. The criteria for including participants in the PTSS group were: 1) endorsement of a traumatic event (Barzilay et al., 2019); 2) presence of re-experiencing symptoms (nightmares/flashbacks/thoughts OR distress in reminiscent situation); 3) symptom duration of \geq one month; and 4) a distress or impairment score of \geq 5 on a scale of

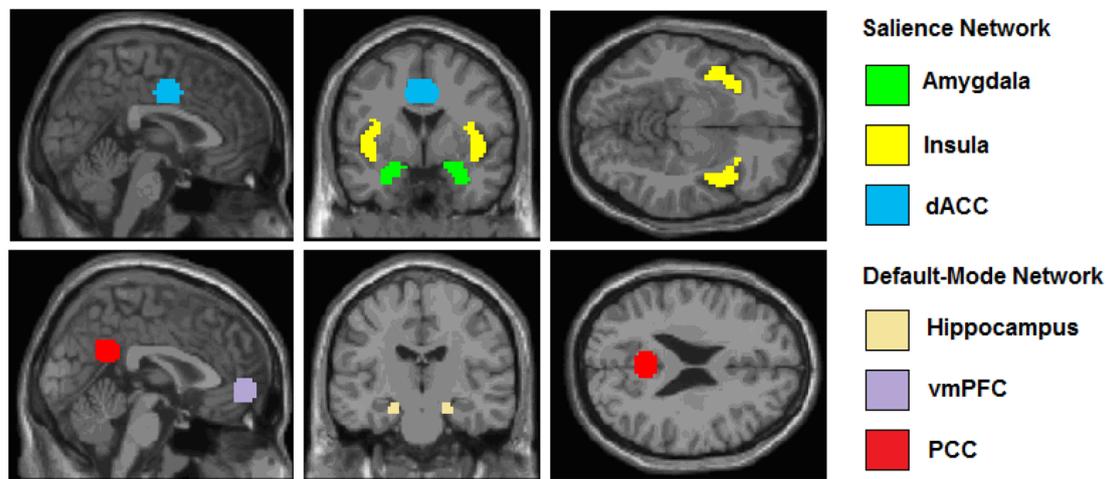


Fig. 1. Visualization of the seeds that were used. Coordinates (De Luca et al., 2006): dACC ($\pm 4, -6, 40$) 10 mm rad sphere; PCC ($\pm 2, -51, 27$) 10 mm rad sphere; vmPFC ($\pm 2, 54, -4$) 10 mm rad sphere; Hippocampus ($\pm 20, -19, -18$) 5 mm rad sphere. Anatomical masks were used for insula (Sripada et al., 2012b) and amygdala (Sripada et al., 2012a).

0–10 using the GOASSESS interview (Barzilay et al., 2019). Participants with psychosis spectrum symptoms were excluded from all groups, and participants with any psychopathology or hospitalization record were excluded from both control groups. Ninety-one participants were excluded due to excessive motion (see below), which resulted in a final sample of $n = 59$ PTSS participants [age (SD) = 17.08 (2.39) years, 71.19% female] and $n = 226$ asymptomatic controls [age (SD) = 15.56 (3.95) years, 51.77% female]. These controls included $n = 73$ TECs [age (SD) = 16.31 (3.55) years, 32.88% female] and $n = 153$ Non-TECs [age (SD) = 15.20 (4.08) years, 60.78% female]. While no difference in motion (based on framewise displacement threshold) was found between the groups ($p = .741$), the groups differed on age and gender ($p = .002$ and $p < .001$, respectively). Age, gender and motion were controlled for in all the analyses.

2.2. Resting-state paradigm

Participants underwent structural MRI (sMRI) and functional MRI (fMRI) scanning that included a resting-state procedure along with other tasks (n-back, emotion identification) reported elsewhere (e.g., Satterthwaite et al., 2014). Participants were positioned in the scanner with their heads comfortably restrained to reduce head movement. Participants lay supine in the MRI scanner and viewed the projected stimuli inside the scanner through a built-in mirror. During the resting-state scan, a white fixation cross was displayed at the center of a black background for 6.2 min. Participants were instructed to relax and keep their eyes open and fixed on the cross.

2.3. fMRI data acquisition and preprocessing

All MRI scans were acquired on a single 3T Siemens TIM Trio whole-body scanner with a 32-channel head coil. T1-weighted anatomic images (acquisition time = 3:28 min, repetition time/echo time (TR/TE) = 1810/3.5 ms, field of view (FOV) = 180×240 mm, and slice thickness = 1 mm, 0 mm gap) were acquired for coregistration. Functional images were acquired with gradient echo blood oxygen level dependent (BOLD) scans (TR/TE = 3000/32 ms, flip angle = 90° , FOV = 192×192 mm, slice thickness = 3 mm, 0 mm gap, and 124 repetitions). Four volumes before the initiation of the rest period were discarded at the beginning of each run to allow for equilibration of the MRI signal. For a full list of fMRI tasks and data acquisition parameters, please refer to Satterthwaite et al. (2014).

The fMRI data were preprocessed using the statistical parametric mapping software package SPM8 (Wellcome Centre for Human Neuroimaging, London, UK). Functional slices within each volume were sinc-interpolated, weighted in time, slice by slice, to correct for the sequence of slice acquisition. The functional volumes were realigned to correct for head motion, and structural images were coregistered to the functional images. The structural images were spatially normalized to a standard MNI template using the voxel-based morphometry toolbox (VBM8 <http://dbm.neuro.uni-jena.de/vbm>) and DARTEL high-dimensional warping. Estimated deformation fields from warping were applied to normalize functional images to MNI space, which were then smoothed using a 5 mm full width at the half maximum (FWHM) Gaussian kernel. Functional data were detrended to account for scanner drift. To control for non-neuronal noise sources due to heart beat, respiration, and motion, we first extracted BOLD time series from sMRI-derived white matter and cerebrospinal fluid masks. A PCA was performed and the top five components of the time series were added to the model as nuisance covariates.

Motion parameters, their first derivatives, and quadratic terms of original and derivatives were used as nuisance covariates to remove signal related to spin history related motion artifacts. Since rsFC measures low-frequency spontaneous BOLD oscillations (0.01 to 0.10 Hz band), the time course for each voxel was band-pass filtered in this range. Finally, due to motion's large potential effects on regional correlation, we performed “scrubbing/censoring” (i.e., excluding volumes) based on a framewise displacement threshold of 0.2 mm. A total of 91 participants' scans, which included less than 4.2 min of “good” data (i.e., without excessive motion), were removed from analysis.

2.4. MRI data analysis

Connectivity analyses were performed using the MATLAB toolbox ConnTool, developed by Robert Welsh (Jelsone-Swain et al., 2010). As our groups differed in age and female-to-male ratio, we included these variables (as well as motion) as nuisance covariates in all our analyses.

2.4.1. Seed-based analysis

We examined rsFC using a priori seeds based on prior literature (De Luca et al., 2006; Sripada et al., 2012a, 2012b) within Saliency Network (SN; insula, amygdala, dorsal anterior cingulate cortex (dACC)) and Default-Mode Network (DMN; posterior cingulate cortex (PCC), ventromedial prefrontal cortex (vmPFC), hippocampus; see

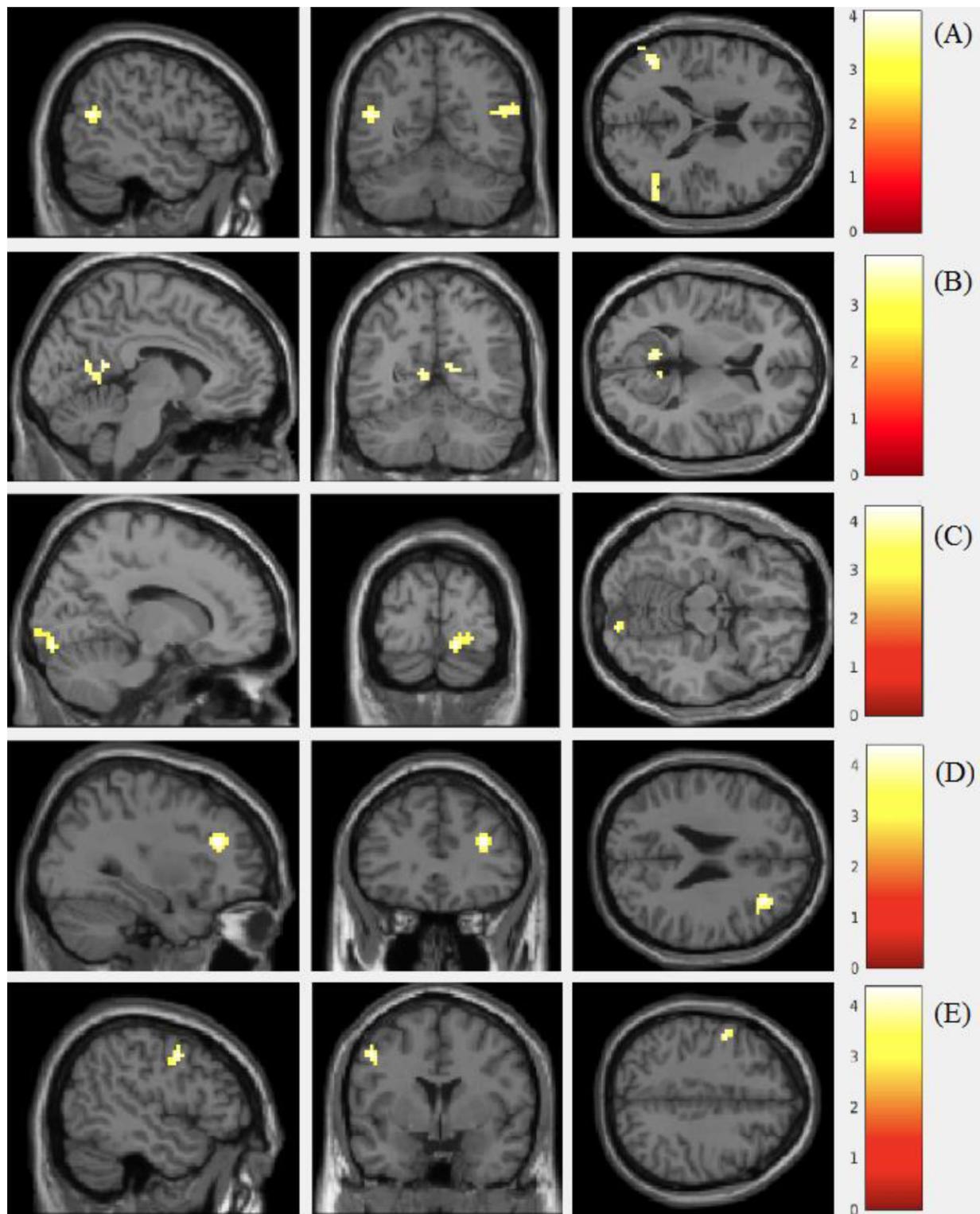


Fig. 2. Comparison of rsFC in PTSS ($n = 59$) vs asymptomatic controls ($n = 226$). (A) Insula seed. PTSS > controls contrast revealed greater SN-DMN connectivity in participants with PTSS between insula and superior temporal sulcus (STS). (B) vmPFC seed. Controls > PTSS contrast revealed less within-DMN connectivity in participants with PTSS between vmPFC and precuneus. (C) dACC seed. PTSS > controls contrast revealed greater SN-VAN connectivity in participants with PTSS between dACC and lingual gyrus. (D) vmPFC seed. PTSS > controls contrast revealed greater DMN-DAN connectivity in participants with PTSS between vmPFC and middle frontal gyrus (MFG). (E) dACC seed. PTSS > controls contrast revealed a trend for greater SN-DAN connectivity in participants with PTSS between dACC and MFG. Only significant or trend-level results are included (all FWE-corrected $p < .100$). Note: In (A) and (B), bilateral connectivity survives $p < .001$ uncorrected threshold but not FWE correction and is shown for visualization only (see Table 1).

Fig. 1). These seeds were used to generate individual-level whole-brain connectivity maps via Pearson product moment correlations resulting in a 3D correlation coefficient image (r -image). R -images were then transformed to z -scores using a Fisher r -to- z transformation. Z -score images from the individual functional-connectivity analyses were entered into second-level random effects analyses (factorial ANOVA and t -tests) implemented in SPM8. We tested how connectivity between the seeds and all other voxels in the brain differed between PTSS and asymptomatic control groups, between TEC and Non-TEC subgroups, and between PTSS and TEC groups. We also tested how these connectivities were correlated with distress and impairment symptoms (a score that combined two GOASSESS questions on a total scale of 0–20) in the PTSS group. Second-level maps were initially thresholded at $p \leq 0.001$ uncorrected, and then a cluster threshold of $p \leq 0.050$ corrected for whole-brain family-wise error (FWE).

We also used the seeds described above to conduct ROI-ROI network analysis to test connectivity within and between DMN and SN, specifically testing connectivity between each of the *a priori* seeds (total of 15 connections). As in the whole-brain seed-based approach, we tested differences between PTSS and all asymptomatic controls, between TEC and Non-TEC subgroups, between PTSS and TEC groups, and correlations with distress and impairment score in the PTSS group. Due to its specificity and the use of *a priori* seeds, the ROI-ROI approach holds greater statistical power to test hypothesized neural alterations than the whole-brain approach.

2.4.2. Exploratory connectome-based analyses

Whole-brain connectomes were generated from 264 putative functional areas (Power et al., 2011). We then utilized graph-theory algorithms to calculate the following whole-brain global metrics from individual-level connectomes: clustering (amount of interconnections between topologically neighboring nodes), characteristic path length and efficiency (related to the shortest length of connection between various nodes within the network), small-worldness (ratio of clustering and path length between the clusters within the network), strength (degree of association between all regions (“nodes”) within the brain network) and modularity (ability of the network to form sparsely interconnected modules, each containing densely intracommunity nodes) (Bullmore and Sporns, 2009). For each metric, we used sparsity thresholds (S ; the fraction of the total number of edges remaining in a network), with a range of $0.10 < S < 0.34$ and an interval of 0.01, consistent with prior studies on adolescent PTSS (e.g., Lei et al., 2015; Suo et al., 2015). The purpose of sparsity thresholds is to address the individual difference in total number of edges, and provide each graph with the same number of edges. Additionally, area under the curve (AUC) was calculated for each network metric (over the sparsity range of thresholds) to derive an integrated score for each measure, independent of a single threshold selection. T -tests were used to test differences between PTSS and all asymptomatic controls, TECs and Non-TECs, PTSS and TECs, and correlations with impairment and distress score, in the AUCs for each of the metrics. In addition to whole brain global metrics, we utilized the same procedures to calculate metrics at the network level for DMN and SN.

Finally, we performed Connectome-based Predictive Modeling (CPM; Shen et al., 2017). Within a 10-fold cross validation, each edge from the generated connectomes was used as a regressor to predict group membership (PTSS vs TEC; TEC vs Non-TEC) across training participants, and a significance threshold of 0.010 was applied to select the most PTSS-related edges. We then summarized the selected edges to a single value per participant (using the sum of all the edge strengths), which was used for model fitting. The models were then applied to generate predicted group probabilities for the held-out subjects. For further details, see Shen et al. (2017).

3. Results

3.1. Posttraumatic stress symptoms group (PTSS; $n = 59$) vs asymptomatic controls ($n = 226$)

3.1.1. Seed-based analysis (Table 1 and Fig. 2)

Saliency Network (SN) seeds: Compared with controls, the PTSS group had greater connectivity between anterior insula seed and the superior temporal sulcus, a region within DMN (Fig. 2A). The PTSS group also had greater connectivity between dACC seed and the lingual gyrus, a region in the VAN (Fig. 2C), and a trend for greater connectivity between dACC seed and the MFG, a region in the DAN (Fig. 2E).

Default-Mode Network (DMN) seeds: Compared with controls, the PTSS group had less connectivity between vmPFC seed and the pre-cuneus, a key DMN region (Fig. 2B). The PTSS group also had greater connectivity between vmPFC seed and the MFG, a region in the DAN (Fig. 2D).

3.1.2. ROI-ROI network analysis (Table 2)

There was a trend-level difference in SN-DMN connectivity, between insula and vmPFC seeds. Specifically, we used univariate ANOVA with insula-vmPFC connectivity as the dependent variable and group (PTSS, controls) as the independent variable, while controlling for age, sex and motion. PTSS participants had greater (less negative) insula-vmPFC connectivity. No differences between the PTSS group and all controls were found with any other ROI-ROI connectivities.

3.1.3. Connectome-based analysis (Table 3)

Graph theory: In the whole-brain analysis, there was a trend-level group difference, with the PTSS group having less global small worldness than controls. In the network-level analysis, consistent with our seed-based findings, the PTSS group showed alterations within DMN. Specifically, we found less efficiency and greater characteristic path length in DMN of participants with PTSS, compared to controls. Several additional findings within DMN approached significance: PTSS group showed less strength, less centrality, and greater modularity. No group differences within SN were observed (all $p > .100$).

Connectome-based Predictive Modeling (CPM): Analysis did not predict group membership better than random chance.

3.2. Trauma-exposed controls (TECs; $n = 73$) vs non-trauma-exposed controls (Non-TECs; $n = 153$)

3.2.1. Seed-based analysis (Table 1 and Fig. 3)

SN seeds: Compared with Non-TECs, TECs had greater connectivity between amygdala and superior parietal lobule (SPL), a region within Dorsal Attention Network (DAN; Fig. 3B).

DMN seeds: Compared with Non-TECs, TECs had lower connectivity between hippocampus and bilateral middle frontal gyrus (MFG), also a region within DAN (Fig. 3A).

3.2.2. ROI-ROI network analysis (Table 2)

There was a difference in the connectivity within SN, between amygdala and dACC seeds. Specifically, we used univariate ANOVA with amygdala-dACC connectivity as the dependent variable and group (TEC, Non-TEC) as the independent variable, while controlling for age, sex and motion. TEC participants had greater amygdala-dACC connectivity. No differences between the control groups were found with any other ROI-ROI connectivities.

3.2.3. Connectome-based analysis (Table 3)

Graph theory: In the whole-brain analysis, there were no differences between TEC and Non-TEC subgroups on any of the global metrics

Table 1

Differences in seed-based connectivity patterns. STS = superior temporal sulcus; vmPFC = ventromedial prefrontal cortex; MFG = middle frontal gyrus; IFG = inferior frontal gyrus; PCC = posterior cingulate cortex; ITG = inferior temporal gyrus; MTG = middle temporal gyrus; dACC = dorsal anterior cingulate cortex; SPL = superior parietal lobule; STG = superior temporal gyrus.

Regions	Networks	Contrast	Figure	Cluster <i>K</i>	MNI [X Y Z]	<i>Z</i> _e	Cluster <i>p</i> (FWE-corrected)
PTSS (n = 59) vs asymptomatic controls (n = 226)							
Insula - STS	SN - DMN	PTSS > Controls	2A	44	-48 -61 16	4.02	.041
				22	57 -58 19	3.58	.349*
vmPFC - precuneus	within DMN	Controls > PTSS	2B	46	-9 -64 13	3.80	.034
				29	6 -52 4	3.80	.175*
dACC - lingual gyrus	SN - VAN	PTSS > Controls	2C	45	15 -88 -14	4.21	.039
vmPFC - MFG	DMN - DAN	PTSS > Controls	2D	49	33 32 25	4.3	.026
dACC - MFG	SN - DAN	PTSS > Controls	2E	37	-48 2 43	4.27	.083
TEC (n = 73) vs Non-TEC (n = 153)							
Hippocampus - MFG	DMN - DAN	Non-TEC > TEC	3A	102	-54 -7 34	4.15	<.001
				39	57 -4 37	3.99	.061*
Amygdala - SPL	SN - DAN	TEC > Non-TEC	3B	44	-39 -43 64	4.05	.040
				28	39 -43 67	3.90	.191*
PTSS (n = 59) vs TECs (n = 73)							
Amygdala - MTG	SN - DMN	PTSS > TEC	4A	40	60 2 -29	3.94	.048
PCC - ITG	within DMN	TEC > PTSS	4B	35	-57 -25 -23	4.06	.090
dACC - lingual gyrus	SN - VAN	PTSS > TEC	4C	69	30 -85 -5	3.80	.005
Hippocampus - IFG	DMN - VAN	PTSS > TEC	4D	58	60 14 13	4.17	.009
PTSS only (n = 59): Correlations with distress and impairment symptoms							
Amygdala - STG	SN - DMN	Negative correlation	5A	66	57 -43 19	4.56	.003
Hippocampus - MFG	DMN - DAN	Negative correlation	5B	38	54 -22 31	4.29	.045
PCC - MFG	DMN - DAN	Negative correlation	5C	62	-60 -7 19	4.59	.006

* Bilateral connectivity survives *p* < .001 uncorrected threshold but not FWE correction.

Table 2

Findings from ROI-ROI network analysis. Only significant or trend-level findings are included (all *p* < .100).

ROIs	Networks	<i>F</i> / <i>r</i>	<i>p</i>
PTSS (n = 59) vs asymptomatic controls (n = 226)			
Insula - vmPFC	SN - DMN	<i>F</i> (1,280) = 3.705	.055
TEC (n = 73) vs Non-TEC (n = 153)			
Amygdala - dACC	within SN	<i>F</i> (1,221) = 4.725	.031
PTSS (n = 59) vs TECs (n = 73)			
None			
PTSS only (n = 59): Correlations with distress and impairment symptoms			
Amygdala - hippocampus	SN - DMN	<i>r</i> (54) = .303	.023
Amygdala - insula	within SN	<i>r</i> (54) = -.253	.060
Amygdala - PCC	SN - DMN	<i>r</i> (54) = -.232	.085

tested. In the network-level analysis, there were alterations within DMN. Specifically, compared to Non-TECs, TEC group showed less clustering, less efficiency and a trend for less strength. There were no group differences on any of the metrics within SN (all *p* > .100).

CPM: Analysis did not predict group membership better than random chance.

3.3. PTSS group (n = 59) vs TEC group (n = 73)

3.3.1. Seed-based analysis (Table 1 and Fig. 4)

SN seeds: Compared with TECs, participants with PTSS had greater connectivity between amygdala and middle temporal gyrus (MTG), a region within DMN (Fig. 4A). The PTSS group also had greater connectivity between dorsal anterior cingulate cortex (dACC) and lingual gyrus, a region within VAN (Fig. 4C).

DMN seeds: Compared with TECs, participants with PTSS had greater connectivity between hippocampus and inferior frontal gyrus (IFG), a region within Ventral Attention Network (VAN; Fig. 4D). The PTSS group also had a trend for lower connectivity between posterior cingulate cortex (PCC) and inferior temporal gyrus (ITG), another region within DMN (Fig. 4B).

3.3.2. ROI-ROI network analysis (Table 2)

No significant differences in connectivity patterns were detected between PTSS and TEC groups for any of the ROI-ROI connectivities, when controlling for age, sex and motion (all *p* > .100).

3.3.3. Connectome-based analysis (Table 3)

Graph theory: In the whole-brain analysis, there were no differences between PTSS and TEC groups on any of the global metrics tested. There were also no group differences on any of the network-level metrics tested (within both SN and DMN; all *p* > .100).

CPM: Analysis did not predict group membership better than random chance.

3.4. PTSS group only (n = 59): correlations with distress/impairment symptoms

3.4.1. Seed-based analysis (Table 1 and Fig. 5)

SN seeds: There was a negative correlation between distress and impairment symptoms, and the connectivity between amygdala and superior temporal gyrus (STG), a region suggested to be part of DMN (e.g., Grimm et al., 2009; Fig. 5A).

DMN seeds: There were negative correlations between distress and impairment symptoms, and the connectivity between hippocampus, PCC and middle frontal gyrus (MFG), a region within DAN (Fig. 5B-C).

3.4.2. ROI-ROI network analysis (Table 2)

Distress and impairment symptoms positively correlated with SN-

Table 3
Graph-theory results. Only significant (bolded) or trend-level findings are included (all $p < .100$).

	PTSS ($n = 59$) vs all controls ($n = 226$)		TEC ($n = 73$) vs Non-TEC ($n = 153$)		PTSS ($n = 59$) vs TEC ($n = 73$)		PTSS only ($n = 59$); correlations	
	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>r</i>	<i>p</i>
Whole brain								
Small-worldness	-1.682	.094	-	-	-	-	-.218	.098
Efficiency	-	-	-	-	-	-	-.232	.077
Path length	-	-	-	-	-	-	.250	.056
Default-Mode Network (DMN)								
Efficiency	-2.542	.012	-2.345	.020	-	-	.149	.012
Strength	-1.820	.070	-1.843	.067	-	-	.108	.070
Path length	1.977	.049	-	-	-	-	-.117	.049
Centrality	-1.738	.083	-	-	-	-	.103	.083
Modularity	1.853	.065	-	-	-	-	-.109	.065
Clustering	-	-	-2.184	.030	-	-	-	-
Saliency Network (SN)								
Path length	-	-	-	-	-	-	-.239	.068
Centrality	-	-	-	-	-	-	.246	.060
Modularity	-	-	-	-	-	-	-.296	.023

DMN connectivity, between amygdala and hippocampus. Symptoms also approached negative correlation with within-SN connectivity, between amygdala and insula, and with SN-DMN connectivity, between amygdala and PCC. All analyses controlled for age, sex and motion.

3.4.3. Connectome-based analysis (Table 3)

Graph theory: In the whole-brain analysis, several trend-level correlations between graph-theory measures and distress and impairment symptoms were found. Specifically, symptoms approached negative correlation with efficiency and small worldness, and positive correlation with path length. In the network-level analysis, there were correlations within DMN. Specifically, symptoms negatively correlated with

path length and positively correlated with efficiency. They also approached negative correlation with modularity and positive correlation with centrality and strength. There were also correlations within SN. Specifically, symptoms negatively correlated with modularity, and approached negative correlation with path length and positive correlation with centrality.

4. Discussion

Our study aimed to identify patterns of resting-state functional connectivity (rsFC) in non-treatment seeking adolescents with posttraumatic stress symptoms (PTSS) compared to asymptomatic controls. We

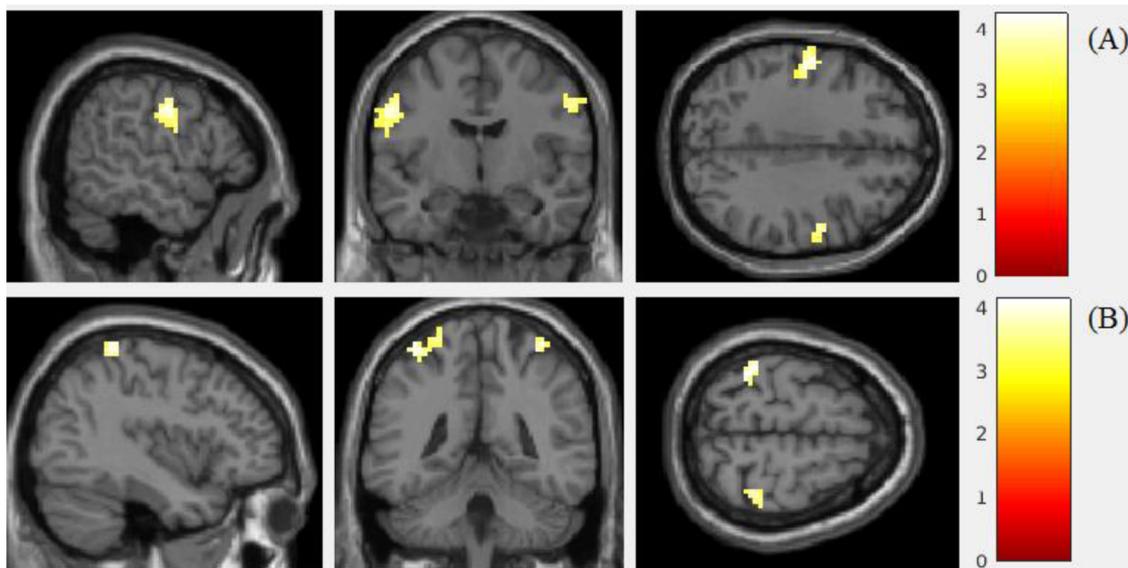


Fig. 3. Comparison of rsFC in TEC ($n = 73$) vs Non-TEC ($n = 153$). (A) Hippocampus seed. Non-TEC > TEC contrast revealed less DMN-DAN connectivity in the TEC group between hippocampus and middle frontal gyrus (MFG). (B) Amygdala seed. TEC > Non-TEC contrast revealed greater SN-DAN connectivity in the TEC group between amygdala and superior parietal lobule (SPL). Only significant results are included (all FWE-corrected $p < .050$). Note: In both (A) and (B), bilateral connectivity survives $p < .001$ uncorrected threshold but not FWE correction and is shown for visualization only (see Table 1).

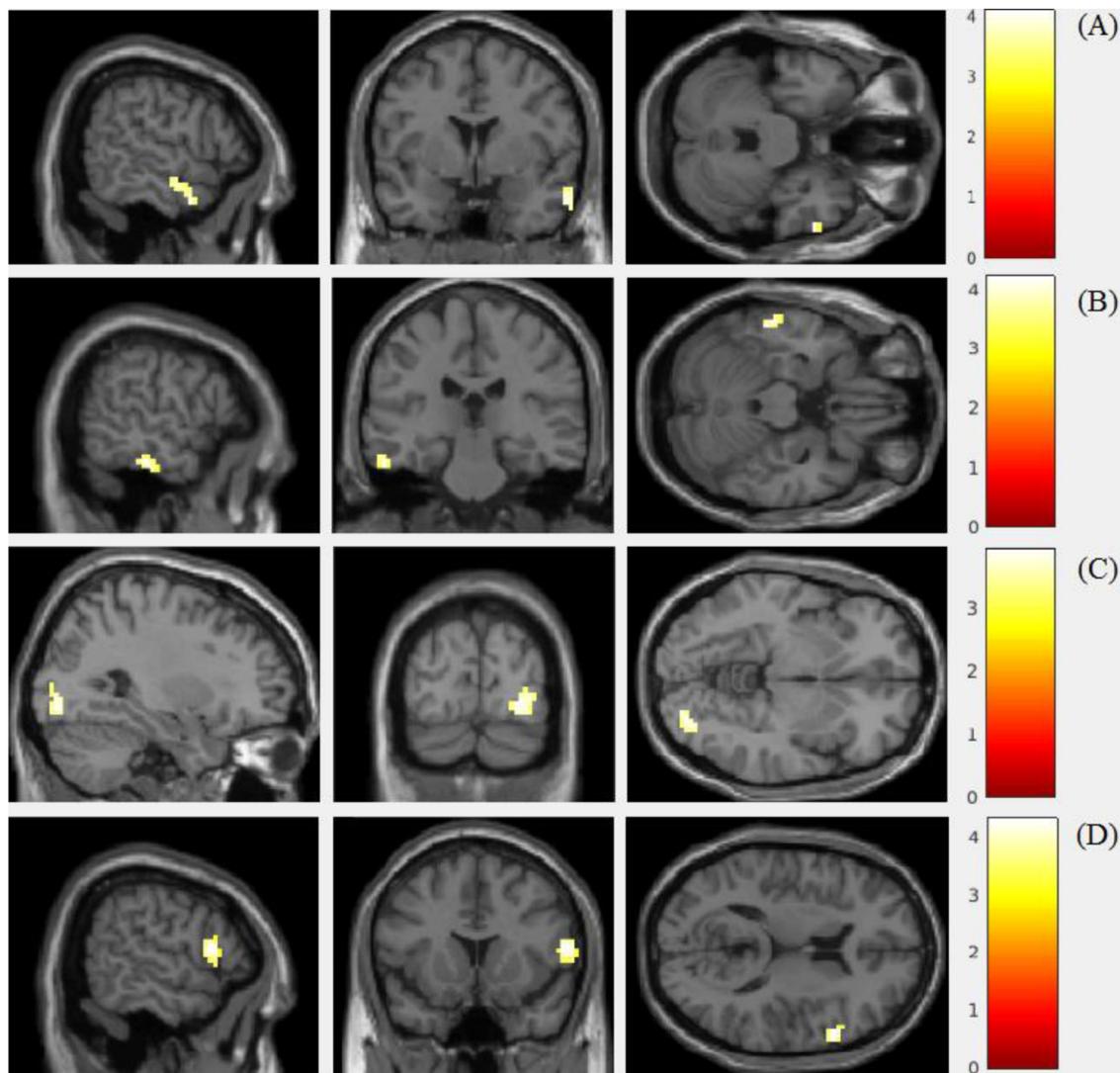


Fig. 4. Comparison of rsFC in PTSS ($n = 59$) vs TECs ($n = 73$). (A) Amygdala seed. PTSS > TEC contrast revealed greater SN-DMN connectivity in participants with PTSS between amygdala and middle temporal gyrus (MTG). (B) PCC seed. TEC > PTSS contrast revealed a trend for less within-DMN connectivity in participants with PTSS between PCC and inferior temporal gyrus (ITG). (C) dACC seed. PTSS > TEC contrast revealed greater SN-VAN connectivity in participants with PTSS between dACC and lingual gyrus. (D) Hippocampus seed. PTSS > TEC contrast revealed greater DMN-VAN connectivity in participants with PTSS between hippocampus and inferior frontal gyrus (IFG). Only significant or trend-level results are included (all FWE-corrected $p < .100$; see Table 1).

combined a series of seed- and connectome-based approaches to replicate potential findings across methods and better understand connectivity characteristics. Consistent with previous findings in adults with PTSD (e.g., Sripada et al., 2012b), our results revealed less connectivity within Default-Mode Network (DMN) and desegregation (greater connectivity) between DMN and Salience Network (SN) in adolescents with PTSS, as compared to asymptomatic controls and trauma-exposed controls (TECs) specifically. In addition, we observed greater DMN-Dorsal Attention Network (DAN) connectivity, greater SN-Ventral Attention Network (VAN) connectivity, and a trend for greater SN-DAN connectivity in the PTSS group compared to asymptomatic controls. Connectome-based analysis confirmed altered rsFC in the PTSS group, and specifically, within DMN. While these patterns of findings in PTSS compared to TEC groups suggest that alterations in connectivity are specific to PTSS symptoms, comparing the TEC and Non-TEC subgroups also suggested that greater within-SN connectivity, altered connectivity between both DMN and SN with attention regions, as well as topological alterations, could be contributed by trauma exposure as well.

Alterations in DMN connectivity have been associated with the pathophysiology of PTSD across many studies (e.g., MacNamara et al.,

2016; Sripada et al., 2012b). In the current study, seed-based analysis revealed weaker within-DMN connectivity (between vmPFC and precuneus) in adolescents with PTSS compared to asymptomatic controls, which is in line with findings from the adult PTSD literature (Akiki et al., 2017; Bluhm et al., 2009; Chen and Etkin, 2013; DiGangi et al., 2016; Shang et al., 2014; Sripada et al., 2012b; Wang et al., 2012; Zhang et al., 2015; Zhou et al., 2012), and suggests that alterations in DMN function in PTSD exist across different age groups, and even in non-treatment seeking subclinical populations. The weaker within-DMN connectivity in the PTSS group compared to TECs, and the lack of such difference when comparing TECs to Non-TECs, suggests that this alteration is associated with PTSD symptom development, rather than trauma exposure per se. Of note, this finding is not consistent with a recent report in slightly younger adolescents (mean age of 14), demonstrating heightened within-DMN connectivity between PCC and inferior frontal gyrus in adolescents with PTSD (Patriat et al., 2016). Additional studies are thus needed to further test and confirm such DMN alterations across development in adolescents with PTSD.

Adolescents with PTSS in our study also exhibited SN-DMN desegregation (greater insula–superior temporal sulcus (STS) and

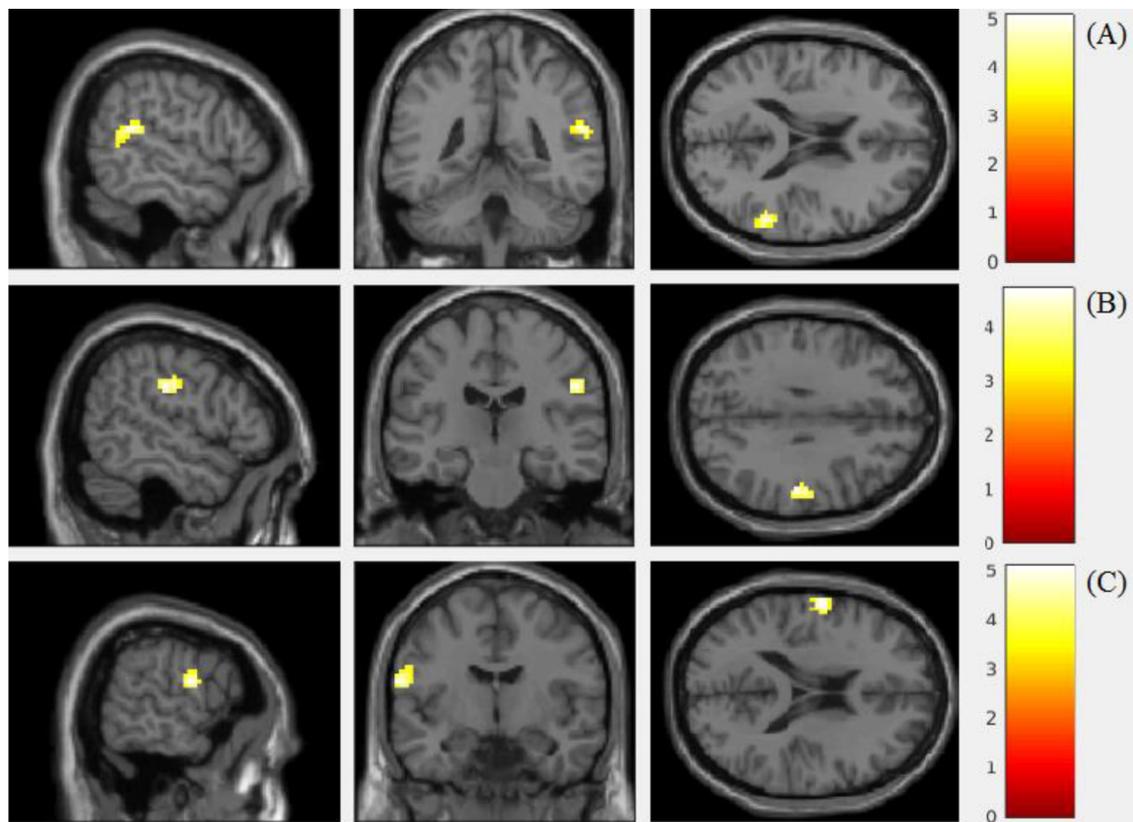


Fig. 5. Correlations between rsFC and distress and impairment symptoms in PTSS group ($n = 59$). (A) Amygdala seed. Distress and impairment symptoms were negatively correlated with SN-DMN connectivity in participants with PTSS between amygdala and superior temporal gyrus (STG). (B) Hippocampus seed. Distress and impairment symptoms were negatively correlated with DMN-DAN connectivity in participants with PTSS between hippocampus and middle frontal gyrus (MFG). (C) PCC seed. Distress and impairment symptoms were negatively correlated with DMN-DAN connectivity in participants with PTSS between PCC and MFG. Only significant results are included (all FWE-corrected $p < .050$; see Table 1).

insula–vmPFC (trend level; $p = .055$) connectivities), which is also consistent with the adult PTSD literature (Block et al., 2017; Brown et al., 2014; Sripada et al., 2012b; Zhang et al., 2015). The greater SN-DMN connectivity in the PTSS group compared to TECs, and the lack of difference when comparing TECs to Non-TECs, suggests that this alteration is also associated with PTSD pathophysiology, independent of trauma exposure. As SN is typically segregated from DMN during rest (Seeley et al., 2007), SN-DMN desegregation might reflect the activation of SN during rest, which in turn, might underlie the hypervigilance and hyperarousal symptoms reported by PTSD patients.

Compared to Non-TECs, the TEC group had greater connectivity between amygdala and dACC, suggesting that trauma alone could contribute to greater within-SN connectivity. This is consistent with a recent report of greater within-SN connectivity in trauma-exposed youth (Marusak et al., 2015), and provides a possible explanation for why some studies did not detect differences in within-SN connectivity when comparing PTSD patients to TECs (e.g., Sheynin et al., 2018). Indeed, some prior reports of greater within-SN connectivity in PTSD included a Non-TEC subgroup, which could have driven this finding (e.g., Abdallah et al., 2019; Sripada et al., 2012b). Our finding is also consistent with the enhanced functional coupling between amygdala and dACC following an acute psychological stress, which was proposed to indicate an extended state of hypervigilance that promotes sustained salience processing, and may play a role in the development of stress-related psychopathologies (van Marle et al., 2010).

The findings of greater SN-VAN and greater (trend-level) SN-DAN connectivity in the PTSS group in our study are consistent with prior findings in adults with PTSD relative to controls (Block et al., 2017). Such findings support the desegregation of various ICNs in PTSD across different age groups, and specifically suggest that greater cross-network connectivity

involving SN might be associated with alterations in attention network functions, which could be associated with impaired disengagement and orienting of attention in PTSD (Block et al., 2017). The finding that connectivity between SN, DMN and VAN was greater in the PTSS group when compared to TECs, and lack of such difference when comparing TEC and Non-TEC groups, suggests that at least some of these altered connectivities with attention regions are associated with PTSD symptoms and are not the result of trauma. Elevated DMN-DAN connectivity was also observed in the PTSS group in our study, which is in contrast to a recent adolescent PTSD report (Patriat et al., 2016). Thus, while the evidence of altered functional connectivity between internally focused thought and attention processing in adolescents with PTSS and PTSD is accumulating, the exact nature of these alterations is still unknown.

Our connectome-based analysis provided supportive evidence for our seed-based findings, examining functional organization across the entire brain and within the networks of interest (SN and DMN). We first followed a graph-theoretical approach to characterize topological properties of the brain (Bullmore and Sporns, 2009). We found greater characteristic path length and less efficiency within DMN in the PTSS group compared to asymptomatic controls, which suggests decreased functional integration of DMN in these participants. It is in line with Akiki et al. (2018) who also found topological DMN alterations in PTSD (less strength and greater modularity – measures that were also found to be altered in the current study (trend-level)), and extends ours and others' seed-based findings of altered DMN connectivity in adults (Akiki et al., 2018; Bluhm et al., 2009; Sripada et al., 2012b) and adolescents (Patriat et al., 2016; Suo et al., 2015) with PTSD. In addition, while our finding of less small-worldness in PTSS (trend-level) adds to the evidence of altered small-worldness in PTSD (Du et al., 2015; Jung et al., 2016; Zhang et al., 2017), such evidence is mixed and

awaits additional investigation. Of note, no topological alterations were found within SN when comparing PTSS and TEC groups, suggesting that group differences in DMN may be more prominently associated with PTSD symptoms. Lastly, we explored the effectiveness of connectome-based predictive modeling (CPM) in this population, but did not find significant predictive models using this approach.

A number of differences in rsFC were found when comparing TECs to Non-TECs. First, while no seed-based differences within DMN were found between these control subgroups, the graph-theoretical measures of efficiency and clustering were lower in DMN in the TEC subgroup. This might suggest that at least some of the within-DMN findings, reported in the PTSD literature, might be related to trauma exposure (in line with DiGangi et al., 2016; Lu et al., 2017). Second, TECs had altered connectivity between SN, DMN and attention regions, and specifically, greater SN-DAN connectivity and less DMN-DAN connectivity. This suggests that trauma exposure could drive some of the altered rsFC patterns between attention networks and SN, or DMN, reported in participants with PTSD compared to controls (Block et al., 2017). Further, the lower DMN-DAN connectivity that was found in TECs compared to Non-TEC is in line with the lower DMN-DAN connectivity recently reported by Patriat et al., when comparing youth with PTSD and Non-TECs (Patriat et al., 2016). Overall, the reported effects of trauma in this study suggest that some, but not all, of the rsFC alterations reported in participants with PTSD are the result of trauma exposure rather than the pathology of PTSD (DiGangi et al., 2016; Lu et al., 2017; Philip et al., 2013). Such differential associations between trauma, PTSS and rsFC could be further investigated in future studies, by recruiting both TEC and Non-TEC groups.

We also analyzed correlations between rsFC measures and self-reported distress and impairment symptoms. The negative correlations between symptoms and DMN-DAN connectivity are consistent with the recent finding that DMN-DAN connectivity is lower in adolescents with PTSD (Patriat et al., 2016). Since such connectivity was also lower in TECs compared to Non-TECs in the present study, our data suggest that both trauma and PTSS could contribute to lower DMN-DAN connectivity in this population. Symptoms were also positively correlated with amygdala-hippocampus connectivity, supporting SN-DMN desegregation in the PTSS group. Additionally, there was a negative correlation between symptoms and amygdala-superior temporal gyrus (STG) connectivity, a region suggested to be part of DMN (e.g., Grimm et al., 2009), possibly providing evidence for the complex connectivity patterns involving these ICNs in PTSD (e.g., see Miller et al., 2017). Correlations with graph-theoretical measures included both positive and negative correlations between distress and impairment and efficiency and path length within DMN, respectively. This adds to a mixed literature on altered characteristic path length in PTSD (Du et al., 2015; Lei et al., 2015; Long et al., 2013), raising the possibility that specific symptoms could contribute to opposing connectivity patterns. Inconsistent results could also stem from the biased range of distress and impairment scores in the current study, as inclusion criteria for the PTSS group included a minimum score of 5 on either one (or both) of these questions. We also found that symptoms were negatively correlated with SN modularity, whereas greater DMN modularity has been recently reported in PTSD (Akiki et al., 2018). Future work is needed to further study the specific associations between topological alterations associated with different PTSD symptoms, to clarify these findings.

A primary strength of this work is that we studied a non-treatment seeking sample of adolescents with PTSS, which allowed us to further assess whether aberrant patterns of rsFC are specific to PTSD or are present in adolescents with subclinical levels of PTSS. Our findings offer strong evidence to suggest that aberrant functioning observed in adults and adolescents with PTSD is also present in adolescents with PTSS, suggesting that changes in neural function can occur before symptoms meet full diagnostic criteria.

Several limitations should be considered when interpreting our findings. While participants in the PTSS group reported significant

PTSD symptoms, formal PTSD diagnoses cannot be established based on the assessments used. Given the nature and aims of the PNC (to conduct a broad and large-scale investigation of adolescent development), PTSD measures were limited to a few questions assessing re-experiencing symptoms, distress, and impairment. However, our findings in adolescents with PTSS replicated, to a large degree, patterns of aberrant connectivity in adults with PTSD, suggesting that large components of functional connectivity differences are present across development and even in those with subclinical symptoms. Future studies examining rsFC in adolescents with PTSD, which utilize full psychiatric diagnostic assessment of PTSD, will be needed to confirm our findings. Due to the cross-sectional nature of the study design, we were unable to examine the time course of trauma exposure, symptom emergence/change, and changes in neural connectivity. Thus, we cannot determine whether the altered neural connectivity in the PTSS group resulted from PTSD symptoms, or whether they were pre-existing risk factors. Longitudinal studies should be developed to answer questions related to change over time in both symptoms and brain function, following trauma exposure.

In conclusion, our findings suggest altered patterns of rsFC in adolescent participants with PTSS, as well as in participants who were exposed to trauma but did not report symptoms, compared to non-trauma-exposed controls. We specifically identified less connectivity within DMN, desegregation between SN and DMN, and greater connectivity between these networks and attention regions in the PTSS group, and greater within-SN connectivity in the TEC subgroup. In addition, graph-theory metrics suggest less efficiency and greater characteristic path length in DMN in participants with PTSS compared to all controls. These patterns of findings in trauma-exposed adolescents are consistent with results reported in the adult PTSD literature and suggest that patterns of rsFC are also associated with partial PTSD symptomatology. In the context of mixed findings in the adolescent PTSD literature, our findings from a large sample add to evidence suggesting similar patterns of connectivity across stages of development. Across several methodological approaches, including seed-based and connectome-based analyses, our results highlight the importance of examining rsFC in DMN and SN as potential mechanisms underlying PTSS and PTSD. They further extend reports that connectivity with attention networks may also play an important role in PTSD development.

CRediT authorship contribution statement

Jony Sheynin: Formal analysis, Writing - original draft. **Elizabeth R. Duval:** Formal analysis, Writing - original draft. **Yana Lokshina:** Formal analysis, Writing - review & editing. **J. Cobb Scott:** Resources, Writing - review & editing. **Mike Angstadt:** Software, Writing - review & editing. **Daniel Kessler:** Software, Writing - review & editing. **Li Zhang:** Formal analysis, Writing - review & editing. **Raquel E. Gur:** Funding acquisition, Resources, Conceptualization, Writing - review & editing. **Ruben C. Gur:** Funding acquisition, Resources, Conceptualization, Writing - review & editing. **Israel Liberzon:** Conceptualization, Supervision, Methodology, Writing - review & editing.

Declaration of Competing Interest

All authors declare no conflict of interests.

Acknowledgments

We would like to thank Kosha Ruparel for assistance with data management and transfer, and Dalia Murra for assistance with imaging analysis. This study was supported by RC2 grants from the National Institute of Mental Health (MH089983, MH089924, T32 MH019112). Dr. Scott's participation was supported by a Department of Veterans

Affairs Career Development Award (IK2CX000772). Daniel Kessler was supported by N.S.F. grant DMS-1646108. Dr. Duval reports funding from NIH (K23MH109762) and the Michigan Institute for Clinical Health Research (UL1 TR000433-10).

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