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Distinct intrinsic network connectivity patterns of post-traumatic stress disorder symptom clusters

Tursich M, Ros T, Frewen PA, Kluetsch RC, Calhoun VD, Lanius RA. Distinct intrinsic network connectivity patterns of post-traumatic stress disorder symptom clusters.

Objective: Post-traumatic stress disorder (PTSD) is considered a multidimensional disorder, with distinct symptom clusters including re-experiencing, avoidance/numbing, hyperarousal, and most recently depersonalization/derealization. However, the extent of differing intrinsic network connectivity underlying these symptoms has not been fully investigated. We therefore investigated the degree of association between resting connectivity of the salience (SN), default mode (DMN), and central executive (CEN) networks and PTSD symptom severity.
Method: Using resting-state functional MRI data from PTSD participants (n = 21), we conducted multivariate analyses to test whether connectivity of extracted independent components varied as a function of re-experiencing, avoidance/numbing, hyperarousal, and depersonalization/derealization.
Results: Hyperarousal symptoms were associated with reduced connectivity of posterior insula/superior temporal gyrus within SN [peak Montréal Neurological Institute (MNI): −44, −8, 0, t = −4.2512, k = 40]. Depersonalization/derealization severity was associated with decreased connectivity of perigenual anterior cingulate/ventromedial prefrontal cortex within ventral anterior DMN (peak MNI: 8, 40, −4; t = −3.8501; k = 15) and altered synchrony between two DMN components and between DMN and CEN.
Conclusion: Our results are consistent with prior research showing intrinsic network disruptions in PTSD and imply heterogeneous connectivity patterns underlying PTSD symptom dimensions. These findings suggest possible biomarkers for PTSD and its dissociative subtype.

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Key words: post-traumatic stress disorders; functional neuroimaging; multivariate analysis; adult survivors of child abuse

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Significant outcomes

- Increased severity of hyperarousal symptoms was associated with decreased connectivity of regions associated with autonomic regulation and somatosensory processing (left posterior insula and superior temporal gyrus) within the salience network (SN).
- Depersonalization/derealization severity was associated with reduced connectivity of regions linked to self-referential processing (perigenual anterior cingulate and ventromedial prefrontal cortex) within the ventral anterior default mode network (DMN).
- As a function of depersonalization/derealization, we observed decreased synchrony between dorsal anterior and posterior DMN components and between the right central executive network (CEN) and ventral anterior DMN.

Limitations

- The results will need to be replicated in a larger sample, to confirm the specificity and generalizability of the findings.
- Due to the cross-sectional study design, we cannot make specific conclusions about the directionality of results.

Introduction

Post-traumatic stress disorder (PTSD) is characterized by an array of cognitive, affective, and attentional disturbances (1–3). However, the neurobiological mechanisms underlying these symptoms are not yet fully understood. Although between-group differences in blood oxygenation level-dependent (BOLD) activation during different tasks have guided understanding of specific task-related abnormalities in neural regions of interest, it is now increasingly recognized that a singular focus on specific brain regions will be inadequate to explain the complex neurobiology underlying psychiatric disorders.

As a result, researchers have begun to characterize sets of functionally connected brain regions (nodes) with temporally correlated patterns of activation into networks called intrinsic connectivity networks (ICNs). These ICNs can be identified during either resting-state or task-specific functional MRI (fMRI) scans (4–6). Menon's (7) triple network model of psychopathology posits that dysfunctional connectivity patterns within and between three key ICNs may underlie much of the affective and neurocognitive symptomatology seen across psychiatric disorders, including PTSD. The three main ICNs include the default mode network (DMN), the salience network (SN), and the central executive network (CEN).

Of the three main ICNs, aberrant connectivity in PTSD populations has been most well-documented within areas of the DMN. Linked to functions such as self-referential processing, autobiographical memory, and emotion regulation (7–9), evidence of resting-state and task-dependent functional connectivity changes within DMN has previously been found in PTSD participants, including altered connectivity between key anterior [e.g., medial prefrontal cortex (PFC) and perigenual/subgenual anterior cingulate cortex (ACC)] and posterior nodes [e.g., posterior cingulate cortex (PCC) and precuneus], as well as other connectivity alterations, including subcortical areas such as hippocampus and thalamus (9–22). Further, overall PTSD symptom severity, as assessed by the Clinician-Administered PTSD Scale (CAPS; 23), has been associated with alterations in resting-state functional connectivity of the PCC/precuneus (DMN seed region), including increased connectivity with precentral sulcus (10), bilateral perigenual ACC, and right amygdala (10, 24), and/or decreased connectivity with left thalamus (14) and left medial PFC (13) and areas of the left and right amygdala (25). Connectivity of DMN seed regions in medial/middle PFC with left hippocampus (10) and right amygdala (15) has also been found to correlate negatively with CAPS scores. One recent study (26) found different connectivity correlations of seed regions in the subgenual ACC with perigenual ACC, as a function of re-experiencing symptoms and with left thalamus, as a function of avoidance/numbing symptoms.

Altered connectivity of the SN, important for identifying personally relevant (salient) internal and external stimuli, and CEN, essential for working memory and executive function, has also been identified in PTSD samples across both resting-state and task conditions (10, 11, 15, 17, 19, 21, 27–35). In particular, fronto-insular areas of the SN are crucial for fluid shifts between DMN and CEN dominance (36, 37), which is thought to represent a key neurofunctional deficit in PTSD (9). Task-related alterations in SN connectivity, including altered coactivation of amygdala, medial PFC, perigenual and subgenual ACC, anterior insula and peri-insula, and parietal regions, have also been associated with PTSD symptom severity, although the direction of these effects has not always been consistent (10, 11, 18, 33).

Despite growing evidence of the multidimensional structure of PTSD (38, 39), few studies to date have attempted to examine differences in connectivity as a function of PTSD symptom clusters (10, 26). Our study further explores this issue through the use of multivariate techniques to isolate the *independent* associations between aberrant functional connectivity and specific PTSD symptom dimensions.

A newly recognized dimension of PTSD symptomatology concerns experiences of depersonalization (i.e., feelings of disconnection from one's

body) and derealization (i.e., the sense that one's surroundings are unreal) (40–43). Such experiences have also been associated with abnormal patterns of functional connectivity during both trauma memory recall and resting-state scans. Specifically, previous work from our group investigating recall of traumatic events found decreased coactivation of the right ACC with right PCC, precuneus, temporal, and occipital areas and with left frontal regions, along with increased connectivity with an inferior frontal area as a function of increased dissociative symptoms (44). Levels of dissociative symptoms also correlated positively with resting-state connectivity between seed regions in the PCC and areas in the right inferior frontal and superior temporal gyri (12).

To date, no prior research has investigated the independent associations of specific domains of PTSD symptomatology (i.e., re-experiencing, avoidance/numbing, hyperarousal, and depersonalization/derealization symptoms) with intrinsic network connectivity. To control for the effects of other covariates, including state anxiety during the scan session and current major depression, we used a multivariate analysis of covariance (MANCOVA) to assess the association of ICNs – derived via independent components analysis (ICA) – with scores on subscales of standard PTSD assessment measures. Specifically, scores pertaining to the dimensions of re-experiencing, avoidance/numbing, hyperarousal, and depersonalization/derealization were extracted from the CAPS (23) and the Multidimensional Dissociation Inventory (MDI; 45). We anticipated that CAPS re-experiencing and hyperarousal symptom clusters would be associated with altered SN connectivity patterns. Because this is a new area of research, these predictions regarding PTSD symptom clusters were primarily theoretically derived, based on known influences of key SN regions in fear conditioning and generally directing attention toward threatening or otherwise emotionally salient stimuli (46, 47). Based on prior research (44, 48), we also hypothesized that there would be significant alterations in DMN connectivity as a function of depersonalization/derealization symptom severity.

Aims of the study

To our knowledge, this is the first study to examine the independent associations between resting-state network connectivity and specific post-traumatic stress disorder symptom clusters. We hypothesized that connectivity changes within the salience network would be associated with re-experiencing and hyperarousal symptoms, while the self-perception alterations characterizing depersonalization/ derealization would be linked to aberrant default mode network connectivity.

Material and methods

Participants and measures

We recruited 21 participants diagnosed with PTSD related to childhood trauma (n = 18 female). All participants had experienced multiple incidents of childhood sexual and/or physical abuse leading to chronic PTSD symptoms, diagnosed using a CAPS (23) clinical cutoff score >50. Comorbid psychiatric conditions were assessed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; 49). Participants with a history of a psychotic disorder, bipolar disorder, recent substance use disorder, head trauma, serious medical illness, or contraindications for research MRI scans were excluded. Demographic information about the sample is provided in Table 1. Half (n = 11) of the participants were prescribed psychotropic medications, including selective serotonin reuptake inhibitors (SSRIs; n = 9), other antidepressants (TCAs; n = 2), anxiolytic/sedatives (n = 4), and/or low-dose antipsychotics for sleep (n = 2). Some participants were prescribed more than one medication concurrently. This study was approved by the Research Ethics Board of the University of Western Ontario as part of an EEG biofeedback study (50). All participants provided written informed consent prior to participating.

Measures and procedures

In addition to the CAPS and SCID-I, participants completed the MDI (45) and Childhood Trauma Questionnaire (CTQ; 51) during the diagnostic assessment interview. State anxiety experienced during the MRI scanning session was measured using the state anxiety portion of the State-Trait Anxiety Inventory (STAI; 52) immediately after completing a 6-min resting-state fMRI scan.

Our variables of primary clinical interest included the CAPS re-experiencing, avoidance/ numbing, and hyperarousal symptom clusters, corresponding to the *DSM-IV-TR* (53) criteria B, C, and D, and depersonalization/derealization symptoms (as measured by the MDI), corresponding with the two major symptoms associated with the dissociative subtype. We used the MDI to measure depersonalization and derealization due to its established psychometric properties (45, 54, 55)

Table 1. Demographic information

	PTSD participants (n = 21)
	M (SD) or n
Age	39.9 (13.7)
CAPS	
Re-experiencing	23.7 (6.8)
Avoidance/Numbing	31.5 (7.3)
Hyperarousal	25.4 (6.0)
Total	80.6 (14.0)
MDI	
Depersonalization/derealization (mean)	11.2 (5.2)
CTQ	
Emotional abuse	17.5 (5.6)
Physical abuse	11.1 (5.3)
Sexual abuse	15.3 (8.2)
Emotional neglect	16.3 (5.2)
Physical neglect	12.6 (5.5)

Axis I comorbidity	Current n	Past n
Major depressive disorder	8	10
Dysthymic disorder	1	0
Panic disorder/agoraphobia	6	4
Social phobia	3	0
Obsessive–compulsive disorder	0	1
Somatization/somatoform disorder	7	1
Eating disorder	2	4

CAPS, Clinician-Administered PTSD Scale; CTQ, Childhood Trauma Questionnaire; MDI, Multiscale Dissociation Inventory; PTSD, post-traumatic stress disorder.

and because it provided more specificity of the symptoms of interest by controlling for the effects of theoretically distinct dissociative presentations (e.g., identity dissociation). We used the arithmetic mean of the MDI depersonalization and derealization subscales because the two were highly correlated in our sample (r = 0.857). All models were statistically controlled for the effects of current major depressive episode, current psychotropic medication use (both coded as present vs. absent), and state anxiety during the scan.

Imaging paradigm and acquisition

MRI data were obtained using a 3.0 Tesla Magnetom Verio scanner (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel phase array head coil. Each participant underwent whole-brain T1-weighted anatomical scans and subsequent T2*-weighted functional resting-state scans, as described previously (50). Structural images used a T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with 1 mm isotropic resolution [TR/TE/TI = 2000 ms/4 ms/900 ms; 90° flip angle; field of view (FOV) = 256 mm × 256 mm; 176 slices, no gap, generalized autocalibrating partially parallel acquisitions (GRAPPA) acceleration = 2]. BOLD fMRI images were collected using a gradient echo planar imaging (EPI) sequence consisting of 60 interleaved slices, 2 mm thick, no gap, positioned parallel to the anterior–posterior commissure line (TR/TE = 3000 ms/20 ms; FOV = 256 mm; 90° flip angle; 2 × 2×2 mm voxel resolution). During the 6 min resting-state scan, participants were instructed to close their eyes and let their minds wander using previously described methods (12, 56). The first four images collected in each run were discarded automatically to allow for equilibration.

Image preprocessing

Preprocessing of images (including slice-timing correction, motion correction, spatial normalization, and smoothing) was performed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) in MATLAB 7.12.0 (MathWorks Inc.) using standard procedures (50, 57). Functional images were normalized using the unified segmentation on T1 image pipeline (58) and smoothed using a full-width half-maximum (FWHM) Gaussian filter of 8 mm. Data were then resliced to Montréal Neurological Institute (MNI) space (3 mm isotropic voxels).

Connectivity analysis

Connectivity analyses of the resting-state data were conducted using the group ICA of fMRI toolbox (GROUPICAT v3.0a/GIFT v2.0a; http://mialab.mrn.org). Based on previous reports regarding the stability of independent components (ICs) as a function of the number extracted (59), we isolated 20 ICs using the Infomax algorithm in GIFT and repeated the estimation 20 times using the ICASSO method (60). We then visually inspected the spatial maps (SM) of all components for the presence of obvious artifacts (e.g., white matter, edges, ventricles, motion related), leaving 15 non-artifactual components for which we had single subject maps and time courses computed within GIFT using back-reconstruction (61). These remaining components were correlated spatially (using Pearson's r) with network templates (for DMN and CEN; available from http://findlab.stanford.edu/functional_ROIs.html; 62) and with network masks from our previous studies (SN; 50, 57). The SN mask was originally derived from the work of Sadaghiani et al. (52), given their observed associations between alpha rhythm and the fMRI SN. Specifically, their findings revealed multiple regions including dorsal ACC, insula, thalamus, and basal ganglia. Subsequently, for this study, we used the ICA mask from our previous studies (40, 47) that had corresponded most closely with the previously described

SN regions (52). In cases where network masks failed to show correlations above $r = 0.5$ for any IC, we used up to three of the most closely correlated ICs, to encompass more of the network.

Finally, we used a multivariate analysis of covariance (MANCOVA) and subsequent *post hoc* univariate analyses, as implemented in the GIFT MANCOVAN toolbox (4), to discover which SM voxels and functional network connectivity (FNC) correlations were uniquely associated with each of our clinical variables of interest, while statistically controlling for the effects of all other clinical variables. The SM correlations provide details on temporal relationships of specific clusters of voxels within the larger ICs (within-network/intranetwork connectivity), while the FNC correlations supply information about the temporal relationships between the separate ICs (between-network/internetwork connectivity; 4). We included all non-artifactual ICA components in the multivariate models, with a significance threshold of $\alpha = 0.05$. After appropriate transformation (FNC correlations were Fisher-transformed), the SM and FNC response matrices were dimension-reduced using a principal components analysis (PCA), as previously described (4), thus reducing each response vector (SM and FNC) to eight principal components. These response vectors were then submitted to the MANCOVA models. However, only those components pertaining to the networks of theoretical interest were further explored using *post hoc* univariate models. To provide an acceptable balance of Type I and Type II error risk for univariate SM comparisons, we used a combined intensity and cluster size of $P < 0.005$ with a 10 voxel extent threshold (63). Due to the novel nature of this study in reporting the effects of PTSD symptom clusters on FNC correlations, we report univariate FNC results using a less conservative threshold of $P < 0.05$, uncorrected. As per previous methods (6), we report these results to provide additional context and to allow for future replication and extension.

Results

Twenty ICs were extracted using ICA, five of which were determined visually to be artifactual. Spatial correlations were then performed using the specified masks (50, 62). Three components were associated with a combined dorsal/ventral DMN mask (IC 8, 4, and 10; $r = 0.386$, 0.283, and 0.219 respectively). As shown in Fig. 1, these components were classified as the posterior DMN (IC 4; consisting primarily of PCC/precuneus and parietal regions), the dorsal anterior DMN (IC 8; consisting primarily of dorsomedial PFC and dorsal cingulate), and the ventral anterior DMN (IC 10; consisting of ventromedial PFC and ventral ACC). Three components showed moderate to high correlations with the CEN mask (IC 14, 3, and 12; $r = 0.469$, 0.391, and 0.313 respectively; see Fig. 1). Of these, IC 14 was primarily located in the left hemisphere, IC 12 in the right, and IC 3 was interhemispheric (see Fig. 1). One component correlated highly with the SN mask (IC 2, $r = 0.884$; see Fig. 2).

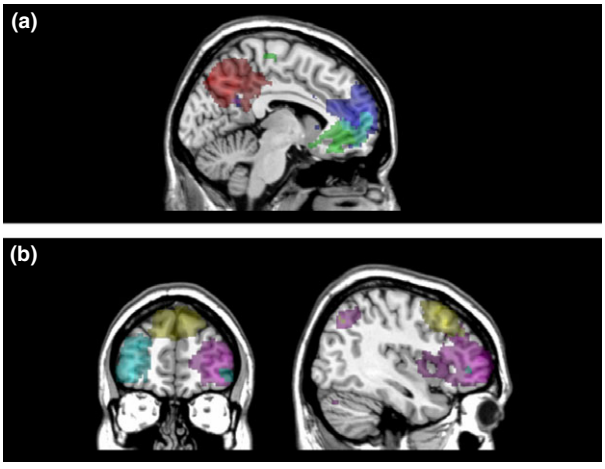

Fig. 1. Independent components (IC) extracted for the default mode (DMN) and central executive networks (CEN). (a) The DMN included posterior (IC 4; pictured in red), dorsal anterior (IC 8; dark blue), and ventral anterior (IC 10; green) components. Overlap between dorsal and ventral anterior DMN is pictured in light blue, and overlap between posterior and dorsal anterior DMN is colored violet. (b) CEN was divided into right (IC 12, magenta), left (IC 14, cyan), and interhemispheric (IC 3, yellow) components. Images were created using MRICRON (http://www.mccauslandcenter.sc.edu/mricro/mricron/).

Intranetwork correlations

Multivariate models included each of the *DSM-IV-TR* PTSD symptom clusters (CAPS re-experiencing, avoidance, and hyperarousal) and MDI depersonalization/derealization symptoms. Variance inflation factor (VIF) estimates for all covariates were within normal limits (VIF < 5.0).

Clinician-Administered PTSD Scale PTSD symptoms. Using a multivariate threshold of $P < 0.05$ in MANCOVA models, we found statistically significant SM correlations of PTSD symptoms within CEN (IC 3), SN (IC 2), and DMN (IC 10). However, in univariate models, only the severity of hyperarousal symptoms showed statistically significant ($P < 0.005$, minimum cluster size = 10 voxels) correlations within the SM comparisons. Specifically, as shown in Table 2, increased

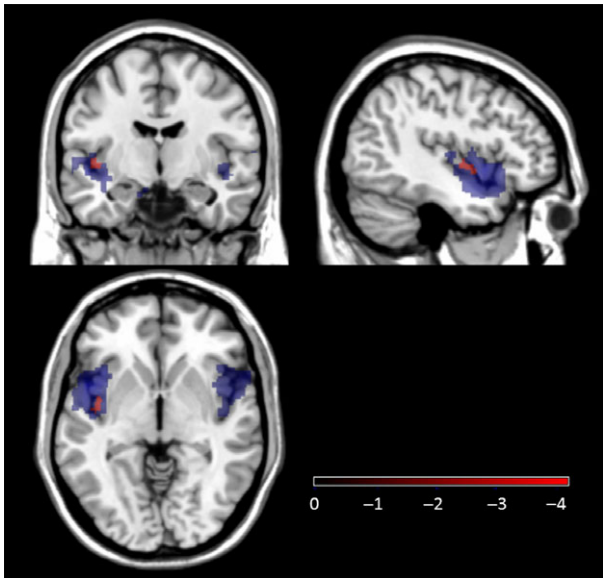

Fig. 2. Regions (in red) displaying decreased connectivity within the salience network (blue) as a function of hyperarousal. Images were created using MRICRON (http://www.mccauslandcenter.sc.edu/mricro/mricron/).

hyperarousal was significantly associated with reduced connectivity of the left posterior insula and superior temporal gyrus within SN (IC 2; peak MNI: −44, −8, 0, $t = -4.2512$, $k = 40$; Fig. 2).

Although significant in the multivariate models, the more stringent univariate criteria for statistical significance reduced the re-experiencing and avoidance/numbing associations to trend-level significance ($P < 0.01$, 10 voxel extent threshold). Specifically, re-experiencing symptoms showed a trend-level correlation toward increased SN connectivity of regions encompassing the left (peak MNI: −52, 6, −8; $t = 2.8061$, $P < 0.01$; $k = 154$) and right (peak MNI: 38, 10, −18; $t = 2.1116$; $P < 0.01$; $k = 57$) superior temporal gyri and ventral anterior insulae [Brodmann's area (BA) 38, 22 and BA 38, 47, for left and right respectively], whereas avoidance/numbing symptoms showed trend-level associations of decreased connectivity of the left superior temporal gyrus, inferior frontal gyrus, and anterior insula (BA 38, 47, 22) within the SN (peak MNI: −48, 6, −8; $t = -3.1935$; $k = 17$) and decreased connectivity of right middle frontal gyrus (BA 8) within the interhemispheric CEN (IC 3; peak MNI: 30, 32, 50; $t = -2.3593$; $k = 18$).

Depersonalization/derealization symptoms. Multivariate models showed statistically significant SM correlations of depersonalization/derealization within the DMN component 10. As shown in Table 2, increased severity of depersonalization/derealization was associated with decreased connectivity of right perigenual ACC and ventromedial PFC within the ventral anterior DMN (IC 10; peak MNI: 8, 40, −4; $t = -3.8501$; $k = 15$; Fig. 3).

Internetwork correlations

Severity of depersonalization/derealization symptoms was significantly associated with decreased

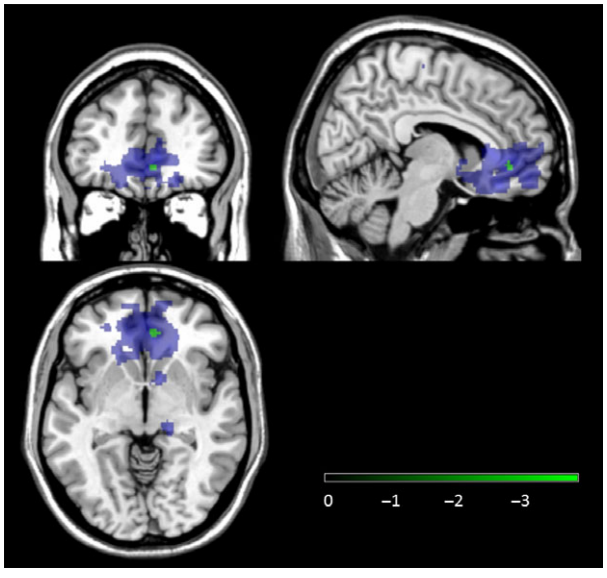

Fig. 3. Clusters (in green) showing decreased connectivity within ventral anterior default mode network (blue) as a function of depersonalization/derealization symptom severity. Images were created using MRICRON (http://www.mccauslandcenter.sc.edu/mricro/mricron/).

Table 2. Spatial map (SM) results

Component	Peak MNI coordinates	Hemisphere	Brain region	Peak intensity *t*-score	Number of voxels
Hyperarousal					
Salience network (IC 2)	−44, −8, 0	L	Posterior insula, superior temporal gyrus, BA 13, 22	−4.2512	40
Depersonalization/derealization					
Ventral anterior default mode network (IC 10)	8, 40, −4	R	Perigenual ACC, ventromedial PFC, BA 32,10	−3.8501	15

ACC, anterior cingulate cortex; AI, anterior insula; BA, Brodmann's area; IC, independent component; MNI, Montréal Neurological Institute; PFC, prefrontal cortex.
All reported SM voxels exceeded the $P < 0.005$, 10 voxel extent threshold.

functional connectivity between dorsal anterior DMN (IC 8) and posterior DMN (IC 4; $P = 0.0002$) and with decreased connectivity between right CEN (IC 12) and ventral anterior DMN (IC 10; $P = 0.016$).

Discussion

To our knowledge, this is the first study to investigate the unique effects of PTSD symptom clusters and dissociative features on functional connectivity within and between the three main ICNs: DMN, CEN, and SN. We found that hyperarousal and depersonalization/derealization symptoms were associated with distinct ICN connectivity patterns, whereas re-experiencing and avoidance/numbing symptoms failed to show statistically significant correlations with ICN SMs.

The finding of altered insula connectivity within SN has previously been described in PTSD, although the overall direction of results has been equivocal. While most studies comparing PTSD participants to controls have reported decreased connectivity of insula from other areas of SN, including amygdala (30, 32), ACC (32, 64), and parietal regions (11), others have found evidence of increased connectivity with other SN regions, such as amygdala (10, 18, 27). Our findings of decreased left posterior insula and superior temporal gyrus integration within SN as a function of hyperarousal symptoms, along with notable opposing trend-level SN associations of overlapping clusters including ventral anterior insula as a function of re-experiencing (increased connectivity) and avoidance/numbing (decreased connectivity), may provide insight into the reasons for the discrepant findings in prior research. The left posterior insula has been implicated in basic sympathetic regulation and visceral/sensory processing, whereas the anterior insula has been more strongly associated with higher-order cognitive and perceptive processing (65, 66). As a result, resting-state posterior insula connectivity may be particularly relevant in the context of the generalized difficulties modulating attention and autonomic arousal characteristic of hyperarousal symptoms (e.g., strong startle response, difficulty concentrating, or sleep problems). Conversely, deficits related to re-experiencing symptoms may be more specific to symptom provocation or other task-based procedures, which may highlight specific functional alterations relevant to such contexts.

In addition, we noted connectivity alterations within ventral anterior DMN (IC 10), as a function of depersonalization/derealization symptom severity. In particular, these dissociative symptoms correlated negatively with functional connectivity of perigenual ACC/ventromedial PFC (BA 32, 10) within the ventral anterior DMN. Increased functional connectivity of perigenual ACC with a DMN seed region in the PCC/precuneus has previously been associated with increased PTSD symptom severity (24). Given the relevance of the DMN and the perigenual ACC to self-referential processing (1, 67), particularly in terms of positive views of oneself (68), it is further intriguing to find here that dissociative symptoms involving severe disruptions of self-perception are associated with decreased functional connectivity of perigenual ACC within the DMN.

The associations of symptom severity with connectivity between ICs (FNC connectivity) revealed additional evidence of disruptions of neural networks in PTSD. Specifically, depersonalization/derealization was associated with reduced FNC connectivity between dorsal anterior DMN and posterior DMN, as well as between the CEN and ventral anterior DMN. These findings are consistent with prior reports of altered connectivity of inferior frontal and superior temporal regions with seed regions in the ACC and PCC as a function of dissociative symptoms (12, 44), although substantial differences in methodology preclude direct comparisons of the direction of this effect.

Implications and limitations

Most of the prior neural network connectivity research in PTSD participants has used region of interest (ROI) or seed-based approaches, which do not allow for the concurrent comparison of multiple networks of interest (69). Using multivariate analyses of ICA components (4, 6, 70), we were able to isolate the associations between functional connectivity patterns and specific symptom types, while statistically controlling for the effects of covariates, including state anxiety, current major depression, and current psychotropic medications. ICA provides several benefits over ROI-based approaches, which require *a priori* specification of seed ROIs. Concerns over the independence of extracted ROI-based functional time courses (and thereby the potential for spurious autocorrelations) are addressed through extracting a set of statistically ICs and simultaneous prewhitening of the data as part of the ICA procedure (71). Additionally, ICA allows for the automatic extraction of artifactual noise into ICs, which is then removed from the analysis. However, the composition of ICA components is sample-dependent and is heavily influenced by the number of components extracted. As found in the present study, nodes

within networks of interest can be distributed over multiple ICs, creating challenges to interpretation of results across different studies.

Our ability to detect clinically relevant correlations between intrinsic network connectivity and PTSD symptom clusters may have been limited by our relatively small sample size ($n = 21$), even if our sample size is comparable to most other studies of functional connectivity in PTSD. Additionally, our sample was composed of mostly women (86%), and many individuals had severe PTSD with a high degree of dissociative symptoms, as well as a high degree of comorbidity. As a result, our findings may not generalize to male samples or to individuals with milder symptom presentations. Finally, half of the participants in our study were prescribed psychotropic medications. Although we included medication use as a covariate in our models, we cannot rule out the potential for undetected influences of medication use on functional connectivity. This fact, as well as the cross-sectional nature of our study, precludes specific conclusions regarding the etiology or directionality of these findings. However, because many patients with PTSD are routinely prescribed psychiatric medications, authors have argued that inclusion of both medicated and unmedicated participants within neuroimaging studies can allow for increased generalizability of neuroimaging data to the overall population of individuals with PTSD (72).

To our knowledge, this is the first study to utilize a multivariate ICA approach for detecting PTSD symptom associations with FNC patterns. Our results confirm prior findings of aberrant connectivity and suggest important differences in the neural substrates underlying specific PTSD symptom clusters. In particular, the findings advance the search for unique biomarkers related to PTSD and its dissociative subtype. Improved understanding of the network abnormalities underlying different features of PTSD is likely to aid both in the development of specific therapeutic interventions targeting these network abnormalities and in assessment of the biological efficacy of such interventions.

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Declaration of interest

The authors do not have any financial interests that might be interpreted as influencing the research.

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