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Structural and Functional Brain Markers of Trauma-related Symptoms

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STRUCTURAL AND FUNCTIONAL BRAIN MARKERS OF TRAUMA-RELATED SYMPTOMS

by

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ABSTRACT

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The neurocircuitry model of posttraumatic stress disorder suggests an association between trauma-related symptoms and abnormalities in the structure and function of limbic and prefrontal brain regions. Evidence also suggests that these structural and functional abnormalities are related. We tested the relation between whole brain white matter integrity, resting-state functional connectivity of a fronto-limbic network, and trauma-related symptoms in 22 trauma-exposed women. We hypothesized that components of whole brain white matter would correlate with components of resting connectivity within a fronto-limbic network. We used parallel independent component analysis (pICA) to test the associations between whole brain fractional anisotropy (FA) maps and resting-state functional connectivity of a fronto-limbic network. We used components extracted from the pICA to predict individual scores on the Clinician-Administered PTSD Scale (CAPS). The pICA identified two independent components from the whole brain FA maps and two independent components from the resting fronto-limbic network, however these components were not significantly correlated across modalities. The two whole

brain white matter components predicted a greater number of PTSD symptoms at a non-significant trend level (R^2 =0.23, $F(3,22)=1.75$, $p=0.193$), and this relationship was driven by a component that represents increased FA of the forceps minor and forceps major. The two resting-state functional connectivity components also predicted greater number of PTSD symptoms at a non-significant trend level ($R^2=0.31$, $F(3,22)=2.69$, $p=0.077$), and this relationship was driven by a component that represents increased resting connectivity within the orbitofrontal and subgenual cortices. Although pICA aims to identify related components across modalities, the components derived here were not significantly related across modalities. Our results suggest that trauma-related symptoms are associated with the structure of two interhemispheric tracts (medium effect size), and the function of a fronto-limbic network (large effect size), and additional analyses are required to further characterize the components extracted from the pICA. Further study of resting-state networks, integrity of pertinent white matter tracts, and their joint relation to trauma-related symptoms would provide a more comprehensive characterization of the mechanisms that underlie trauma-related symptoms. For this reason, multimodal methods such as data fusion represent a valuable tool for the study of trauma-related symptoms and associated structural and functional abnormalities.

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1. Introduction

Trauma exposure and trauma-related symptoms are associated with differences in the structure and function of the brain. The neurocircuitry model of posttraumatic stress disorder (PTSD), which is predominantly supported by evidence drawn from brain activity under task, suggests that trauma-related symptoms are associated with abnormalities in limbic and prefrontal regions (e.g., Patel et al., 2012). The model suggests hyperactivity of the amygdala, which is associated with trauma-exposure and may relate to certain trauma-related symptoms (e.g., hypervigilance; Kleshchova et al., 2019). Beyond task-based evidence, the neurocircuitry model of PTSD is supported by structural evidence of the white matter tracts that connect limbic and prefrontal regions (e.g., Daniels et al., 2013; Koch et al., 2016), as well as the resting-state activity of limbic and prefrontal regions (e.g., Zhu et al., 2017).

Resting connectivity evidence in support of the neurocircuitry model of PTSD involves cortical and subcortical regions. Specifically, trauma exposure is associated with differences in the resting-state functional connectivity of the amygdala (e.g., Kleshchova et al., 2019; Wang et al., 2020), anterior cingulate cortex (ACC; e.g., Chen et al., 2019), and subregions of the prefrontal cortex, such as the orbitofrontal cortex (OFC; e.g., Zhu et al., 2017). The amygdala is involved in affective processing (e.g., Morrison & Salzman, 2010), and the OFC has been implicated in modulation of amygdala activity (e.g., Wager et al., 2008). The ACC monitors the affective salience of stimuli and is involved in regulation of the autonomic nervous system (e.g., Gasquoine et al., 2013). In line with the neurocircuitry model of PTSD, trauma exposure is associated with decreased resting connectivity between the amygdala and OFC (Ke et al., 2017; Zhu et al., 2017). Functional evidence that is inconsistent with this model does however exist, and includes reports of stronger resting connectivity between the amygdala and subgenual ACC

(e.g., Thomason et al., 2015) when trauma-exposed people are compared to controls. Collectively, the amygdala, subgenual ACC, and OFC form an intrinsic connectivity network (ICN; Laird et al., 2011), which is a fronto-limbic network measurable at rest and during task.

Structural evidence in support of the neurocircuitry model of PTSD involves a number of white matter tracts within the brain. Trauma-exposed and non-trauma-exposed people differ in the white matter integrity of the uncinate fasciculus (UF), cingulate part of the cingulum (CGC), and corpus callosum (CC; e.g., O'Doherty et al., 2017). The UF and CGC are association tracts that are involved in regulation of affect (e.g., Keedwell et al., 2016; von Der Heide et al., 2013), and the CC provides interhemispheric projections that include connections between prefrontal and temporal cortices (Roland et al., 2017). The UF carries information bidirectionally between structures of the temporal lobe and the OFC and serves to connect limbic structures with prefrontal regions (e.g., von Der Heide et al., 2013). The fibers of the CGC course through sections of the ACC and the prefrontal cortex (e.g., Heilbronner & Haber, 2014).

The structural evidence that supports the neurocircuitry model of PTSD is however inconsistent in terms of direction. Greater (e.g., Kennis et al., 2015) as well as lesser (e.g., Hu et al., 2016) white matter integrity in the CGC, the UF (e.g., Koch et al., 2017; Yoon et al., 2017), and the CC (e.g., Rinne-Albers et al., 2016; Graziano et al., 2019) have been reported when trauma-exposed people are compared to controls. The inconsistency of the literature might reflect the complexity of trauma and trauma-related symptoms (e.g., context of trauma, severity of symptoms; see Siehl et al., 2018 for review), though insufficient statistical power may also be a factor (Button et al., 2013).

Previous reports of the relationship between trauma-related symptoms and the structure and function of affective brain regions are inconsistent in terms of direction. Structural and

functional differences that are associated with trauma-related symptoms have however been found to be interrelated. Less structural connectivity of the cingulum and less resting connectivity between the hippocampus and ACC have been reported when trauma exposed participants with PTSD are compared to trauma exposed controls (Fani et al., 2016). Therefore, a multi-method approach might provide a more comprehensive and consistent interpretation of the mechanisms that underlie trauma-related symptoms. Incorporation of measures that assess the structural integrity of the brain along with measures of the functional connectivity of a fronto-limbic network would allow for a more complete characterization of the interrelated structural and functional mechanisms that underlie trauma-related symptoms and testing of the neurocircuitry model of PTSD.

Parallel independent component analysis (pICA) is a multimodal approach that can increase statistical power to detect relationships across data types (Calhoun et al., 2016). As a data fusion method, pICA incorporates simultaneous multivariate analysis across modalities, such as diffusion-weighted and resting-state functional data (Calhoun et al., 2008). In this extension of ICA, independent components are extracted from each data source in a process that requires no a priori knowledge of the relationship between modalities. The pICA approach, like ICA, allows data driven identification of independent components in the data, and identifies relationships between components across data types (Calhoun et al., 2009). Previously, pICA has been used to combine structural and functional magnetic resonance imaging (fMRI) data, such as gray matter volume and fMRI task images (Calhoun et al., 2006). We used pICA to extract related (i.e., correlated) components from diffusion-weighted and resting-state functional images.

We tested the degree to which resting-state functional connectivity of a fronto-limbic network, comprised of the bilateral subgenual ACC, amygdala, and OFC, can be decomposed

into components that vary jointly with components from whole brain measures of white matter integrity. We additionally tested the relation between individual subject loadings that correspond to these components and trauma-related symptoms. We did not make predictions in regard to the relation between component loadings and trauma-related symptoms, because the derived components could not be known a priori. While these analyses are considered exploratory, we are interested in testing, for example, if increased connectivity of the amygdala relates to greater trauma-related symptoms.

2. Method

2.1 Participants

We recruited 22 trauma-exposed women ages 18-29 (age: *M*=21.5, *SD*=2.8). We recruited from an urban university in the northeastern US based on responses to an online version of the Life Events Checklist, a 17-item self-report measure for exposure to potentially traumatic events (Gray et al., 2004; see Table 1 for demographic information). Exclusion criteria were age over 30, male gender, MRI incompatibility, and left-handedness. We excluded women older than 30 to avoid confounding effects related to age dependent maturation of brain networks (e.g., Varangis et al., 2019). We excluded men to avoid the confounding effects of sex on trauma-related symptoms, given the well documented sex differences in rates of trauma-related psychopathology (e.g., Breslau, 2009). We excluded left-handed women to avoid confounding effects of lateralization on brain network connectivity (e.g., Pool et al., 2015). We assessed trauma exposure using Criterion A of the PTSD module of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), which defines trauma exposure as an event that involves actual or perceived threat to life or physical integrity of self or others and elicits intense fear, helplessness, or horror.

2.2 Procedure

Participants completed two study sessions: a lab visit that included a structured clinical interview and an MRI scan. The study protocol was approved by the Institutional Review Board and carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2.1 Clinical interview

After informed consent, participants completed a structured clinical interview that included the Clinician-Administered PTSD Scale (CAPS-5; Weathers et al., 2014). We used the CAPS to assess traumatic event details including the timing and type of trauma experienced, as well as the severity and frequency of trauma-related symptoms (e.g., re-experiencing, hyperarousal). We assessed trauma exposure, symptom count, and symptom severity. We also collected information regarding hormonal contraceptive and psychotropic substance use because of evidence that their use affects functional connectivity (e.g., McCabe et al., 2011; Peper et al., 2011).

Table 1.

Participant characteristics (n = 22)

Age in years, *M* (*SD*), range	21.5 (2.8), 18-29
Race/ethnicity, *n* (%)	
Asian/Pacific Islander	7 (32)
Black, non-Hispanic	2 (9)
Hispanic	6 (27)
White, non-Hispanic	6 (27)
Multiple	1 (5)
Index trauma type, *n* (%)	
Sexual assault	9 (41)
Physical assault	6 (27.5)

Assault with weapon	2 (9)
Fire/explosion	1 (4.5)
Sudden, unexpected death of loved one	1 (4.5)
Natural disaster	1 (4.5)
Other unwanted sexual experience	1 (4.5)
Other very stressful event	1 (4.5)
Total number of PTSD symptoms, *M* (*SD*), range	5.9 (4.7), 0-17
Total severity of PTSD symptoms, *M* (*SD*), range	14.8 (10.3), 0-32
Oral contraceptive use, *n* (*%*)	6 (27.3)
Psychotropic substance use, *n* (*%*)	5 (22.7)

2.2.2 MRI scan

The MRI scan included a set of high-resolution structural scans (~13 min), spin echo scans (~1 min), diffusion weighted scans (~9 min), and a 7-min resting scan, during which the participants were instructed to keep their eyes fixated on a white cross on a black background and let their minds wander. We acquired imaging data using a 64-channel gradient head coil on a Siemens MAGNETOM Prisma 3T MRI scanner and a novel Human Connectome Project-like data acquisition protocol (Glasser et al., 2016). We acquired a T1-weighted (T1w) image using the MPRAGE sequence (TR/TE/flip angle=2.4s/2.28ms/8°; FOV=256x256mm; voxel size=0.8mm^3). We acquired a T2-weighted (T2w) image using the variable flip angle turbo spin-echo SPACE sequence (TR/TE=3.2s/565ms; FOV=256x256mm; voxel size=0.8mm^3). We acquired resting-state functional data using multiband image acquisition and a gradient-echo, echo-planar imaging (EPI) T2*-weighted sequence (TR/TE/flip angle=995ms/34ms/52°; FOV=208x208mm; voxel size=2mm^3; MB=6; 425 volumes). We acquired two spin echo fieldmaps using parameters that match the resting-state functional scan parameters. We acquired diffusion MRI whole brain diffusion-weighted images using a spin-echo, echo-planar sequence

along 70 diffusion gradient directions with a b value of 1000s/mm^2 (TR/TE/flip angle = 3.2s/63 ms/78°, b value = 1000s/mm^2, FOV=236x236 mm^2, voxel size=2mm^3; MB=3). We acquired six normalization images with no diffusion encoding (b value = 0) interspersed throughout the scan.

2.3 MRI data preprocessing

We preprocessed imaging data using the Human Connectome Project's minimal preprocessing pipelines (v 3.27.0, Glasser et al., 2013). We aligned each frame of the fMRI timeseries for each subject to a single-band reference image acquired at the start of each scan using a 6-degree-of-freedom registration via FSL's Linear Image Registration Tool (FLIRT) to correct for subject motion. We corrected for distortions in the reference image using estimates of the distortion field derived from the spin echo images. We then registered the reference image to the T1w image using a 6-degree-of-freedom registration via FLIRT. We applied all transformations to the original fMRI timeseries using a single spline interpolation, which included a final transform to a standard-space MNI152 T1 2mm template. We further processed functional data using FSL's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC; Beckmann & Smith, 2004) to clean the functional images of hardware artifacts, participant movement, and physiological noise. Functional data were smoothed with a Gaussian kernel of full width at half maximum=2mm.

We corrected diffusion images for eddy current-induced distortions and adjusted the gradient directions (bvecs) to account for the image rotation conducted during this stage. Afterward, we conducted automated quality control using EDDY QC to detect outlier slices at the subject and group level (Bastiana et al., 2019). We then computed scalar maps of fractional anisotropy (FA). We registered whole brain FA maps to the FMRIB-58 template using FSL's Non-linear Image Registration Tool (FNIRT; Jenkinson et al., 2002).

2.4 Data analysis

2.4.1 Intrinsic connectivity network

Data were analyzed using FSL (version 5.0.9) and MATLAB (R2019b) software packages. We back-reconstructed subject-level estimates of an ICN using a template from Laird et al. (2011). The ICN template we used was derived from an ICA applied to resting-state functional data from the BrainMap database (Laird et al., 2005), and is a spatial map representing coactivation of the ICN comprised of the bilateral subgenual ACC, amygdala, and OFC. We applied MELODIC's dual regression utility to generate subject level estimates of this out of sample ICN. We included the ICN estimates in the pICA, along with each participant's whole brain FA map.

2.4.2 Parallel independent component analysis

We used the Fusion Interface Toolbox (FIT) running on MATLAB (R2019b) to conduct the pICA (Calhoun et al., 2006; Liu et al., 2009). pICA performs simultaneous ICA of the ICN estimates and whole brain FA maps, incorporating a coefficient that represents the Pearson correlation between modalities across subjects. The correlation coefficient is used to update the de-mixing matrices of the two ICAs being conducted in parallel. The output of the pICA consists of spatial maps of ICs from both modalities paired based on correlation, along with values representing the cross-modality correlation strength and significance of these paired ICs (Calhoun et al., 2009). We estimated the dimensionality of the whole brain FA maps and ICN estimates using the minimum description length utility included in FIT, yielding two ICs per modality. We used Bonferroni correction to adjust significance values for all possible cross-modality component correlation pairings (Pearlson et al., 2015). After correction, a significance threshold of $0.05/4 = 0.0125$ was set. We then estimated ICs from each modality by averaging

twenty ICAs to ensure the stability of the components (Meier et al., 2012). Finally, we generated subject by IC matrices, each of which contained the subjects' respective loading coefficients for each IC.

2.4.3 Robust linear regression

We tested the relation between individual subject loadings corresponding to the whole brain FA maps and fronto-limbic ICN resting-state connectivity components and trauma-related symptoms using robust linear regression. We used the bi-square weighting function included in the MATLAB Statistics Toolbox to minimize the influence of outliers (Poldrack, 2012). We used subject loading coefficients for the ICs of the ICN estimates and whole brain FA maps as predictor variables and CAPS symptom count and CAPS symptom severity as outcome variables.

3. Results

3.1 Parallel ICA results

Two FA and two ICN ICs were extracted from the pICA. Pearson correlation values are given for the components paired during extraction. None of the cross-modality IC pairs were significantly correlated (Table 2). To emphasize prominent voxel contributions of each IC, we thresholded the corresponding spatial maps of loading parameters to retain voxels of $|z| > 1.96$ (Figures 1-4; Meier et al., 2012).

IC 1 of the ICN predominantly featured positive clusters in the right frontal orbital and subcallosal cortices (Figure 1; Table 3), and IC 2 of the whole brain FA predominantly featured positive clusters overlapping with the forceps minor and forceps major (Figure 4; Table 3). IC 2 of the ICN predominately featured positive and negative clusters in subcallosal cortex (Figure 2; Table 4), and IC 1 of the whole brain FA predominately featured a positive cluster overlapping

with the forceps minor and negative clusters overlapping with the left superior longitudinal fasciculus, right superior longitudinal fasciculus, and forceps minor (Figure 3; Table 4). Tables 3 and 4 show location and peak statistics of clusters twenty voxels in size or greater that comprise the paired ICs.

Table 2.

Paired independent component correlations

ICN	FA	*r*	*p*-value
1	2	0.33	0.14
2	1	0.24	0.28

Pearson correlation values are shown for paired independent components. Corrected significance threshold was set to p < 0.0125.

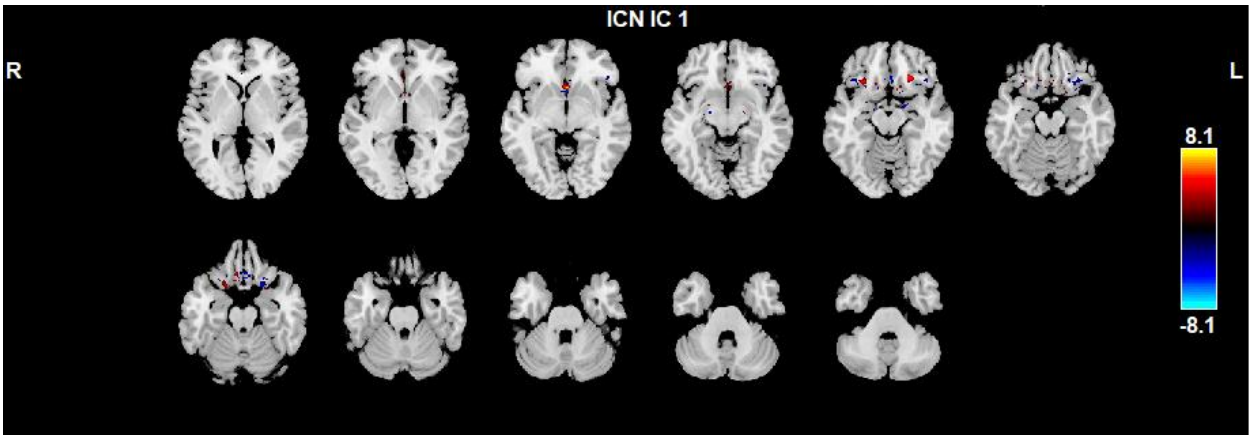

Figure 1. Spatial map of intrinsic connectivity network independent component 1 shown in MNI standard space. Cluster forming threshold: |z| > 1.96. Colorbar indicates z-scored loading parameters of each voxel within the independent component.

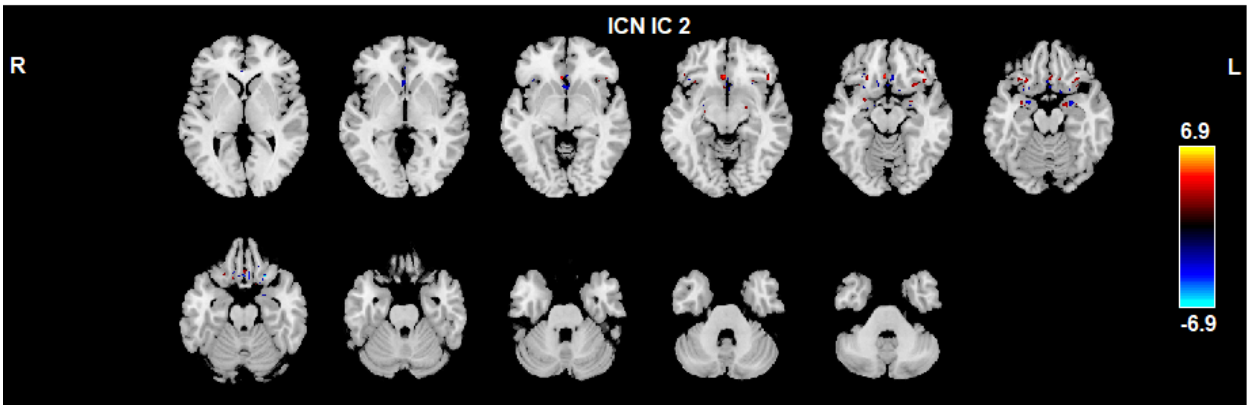

Figure 2. Spatial map of intrinsic connectivity network independent component 2 shown in MNI standard space. Cluster forming threshold: |z| > 1.96. Colorbar indicates z-scored loading parameters of each voxel within the independent component.

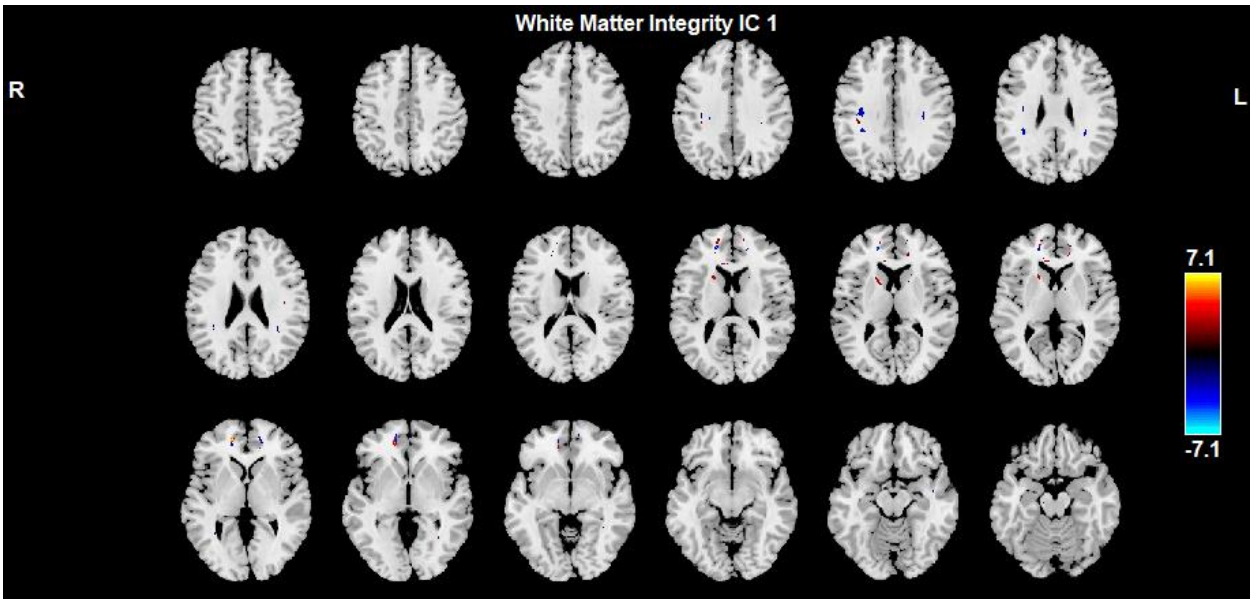

Figure 3. Spatial map of whole brain fractional anisotropy independent component 1 shown in MNI standard space. Cluster forming threshold: |z| > 1.96. Colorbar indicates z-scored loading parameters of each voxel within the independent component.

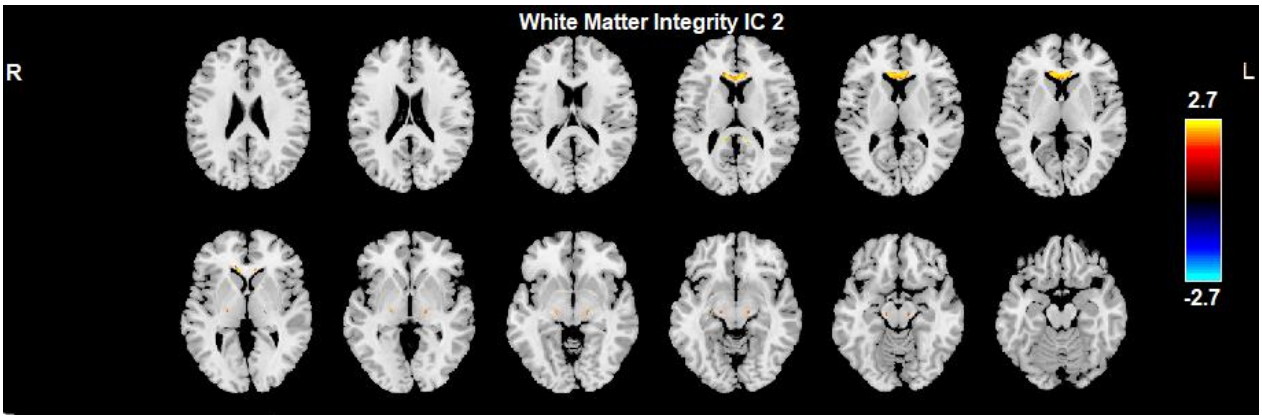

Figure 4. Spatial map of whole brain fractional anisotropy independent component 2 shown in MNI standard space. Cluster forming threshold: |z| > 1.96. Colorbar indicates z-scored loading parameters of each voxel within the independent component.

Table 3.

Cluster and peak statistics for ICN independent component 1

Region	No. of Voxels	z-value	x	y	z
R Frontal Orbital Cortex	38	4.41	-22	30	-18
Subcallosal Cortex	28	7.12	2	18	-8
Cluster and peak statistics for whole brain FA independent component 2					
Region	No. of Voxels	z-value	x	y	z
Forceps Minor	938	2.24	-8	25	14
Forceps Major	313	2.49	13	-42	11

Cluster and peak statistics are shown for paired independent components. Coordinates are given in millimeters within MNI standard space. Statistics are shown for clusters greater or equal to 20 voxels in size.

3.2 Component-symptom relationships

A robust regression model using ICN component 1 and 2 loadings as predictor variables and PTSD symptom count as the outcome variable resulted in a large predictive effect size (R^2=0.31, F(3,22)=2.69, p=0.077; Table 5; Figure 5). A second robust regression model using ICN component 1 and 2 loadings as predictor variables and PTSD symptom severity as the

outcome variable resulted in a medium predictive effect size (R^2 = 0.16, F(3,22) = 1.11, p = 0.37; Table 5; Figure 6). Medication use was included as a covariate in all models.

A third robust regression model using whole brain FA component 1 and 2 loadings as predictor variables and PTSD symptom count as the outcome variable resulted in a medium predictive effect size (R^2 = 0.23, F(3,22) = 1.75, p = 0.193; Table 6; Figure 7). A fourth robust regression model using whole brain FA component 1 and 2 loadings as predictor variables and PTSD symptom severity as the outcome variable resulted in a medium predictive effect size (R^2 = 0.16, F(3,22) = 0.92, p = 0.442; Table 6; Figure 8).

Table 4.

Cluster and peak statistics for ICN independent component 2

Region	No. of Voxels	z-value	x	y	z
Subcallosal Cortex	29	4.58	2	18	-8
Subcallosal Cortex	27	-5.32	0	22	-24
Cluster and peak statistics for whole brain FA independent component 1					
Region	No. of Voxels	z-value	x	y	z
Forceps Minor	259	6.18	-16	49	-1
L Superior Longitudinal Fasciculus	192	-3.57	-35	-19	34
L Superior Longitudinal Fasciculus	189	-4.87	-33	-40	30
Forceps Minor	176	-4.84	-16	49	10
Forceps Minor	162	-4.65	-15	53	-3
R Superior Longitudinal Fasciculus	125	-3.54	33	-43	28
L Anterior Thalamic Radiation	98	3.45	-19	13	10
L Superior Longitudinal Fasciculus	59	3.07	-35	-28	36
L Inferior Fronto-occipital Fasciculus	53	3.33	-32	-63	-2
Forceps Minor	44	3.07	16	42	6
R Inferior Fronto-occipital Fasciculus	39	-2.75	45	-3	-22
Forceps Minor	38	-3.61	15	53	1

Forceps Minor	37	3.72	-7	33	6
R Superior Longitudinal Fasciculus	34	-2.38	35	-22	33
Forceps Minor	32	3.59	15	52	6
Forceps Minor	30	-3.17	-21	40	16
Forceps Minor	28	3.03	-7	31	12
Forceps Minor	27	3.03	-17	43	11
L Inferior Fronto-occipital Fasciculus	22	-2.47	-36	-51	-1

Cluster and peak statistics are shown for paired independent components. Coordinates are given in millimeters within MNI standard space. Statistics are shown for clusters greater or equal to 20 voxels in size.

Table 5.

Robust regression results for ICN ICs and trauma-related symptom count

Predictor	*ß* estimate	*t*-statistic	*p*-value
ICN IC 1	-0.53	-2.45	0.245
ICN IC 2	0.29	1.35	0.195

Robust regression results for ICN ICs and trauma-related symptom severity

Predictor	*ß* estimate	*t*-statistic	*p*-value
ICN IC 1	0.26	1.04	0.31
ICN IC 2	0.36	1.46	0.163

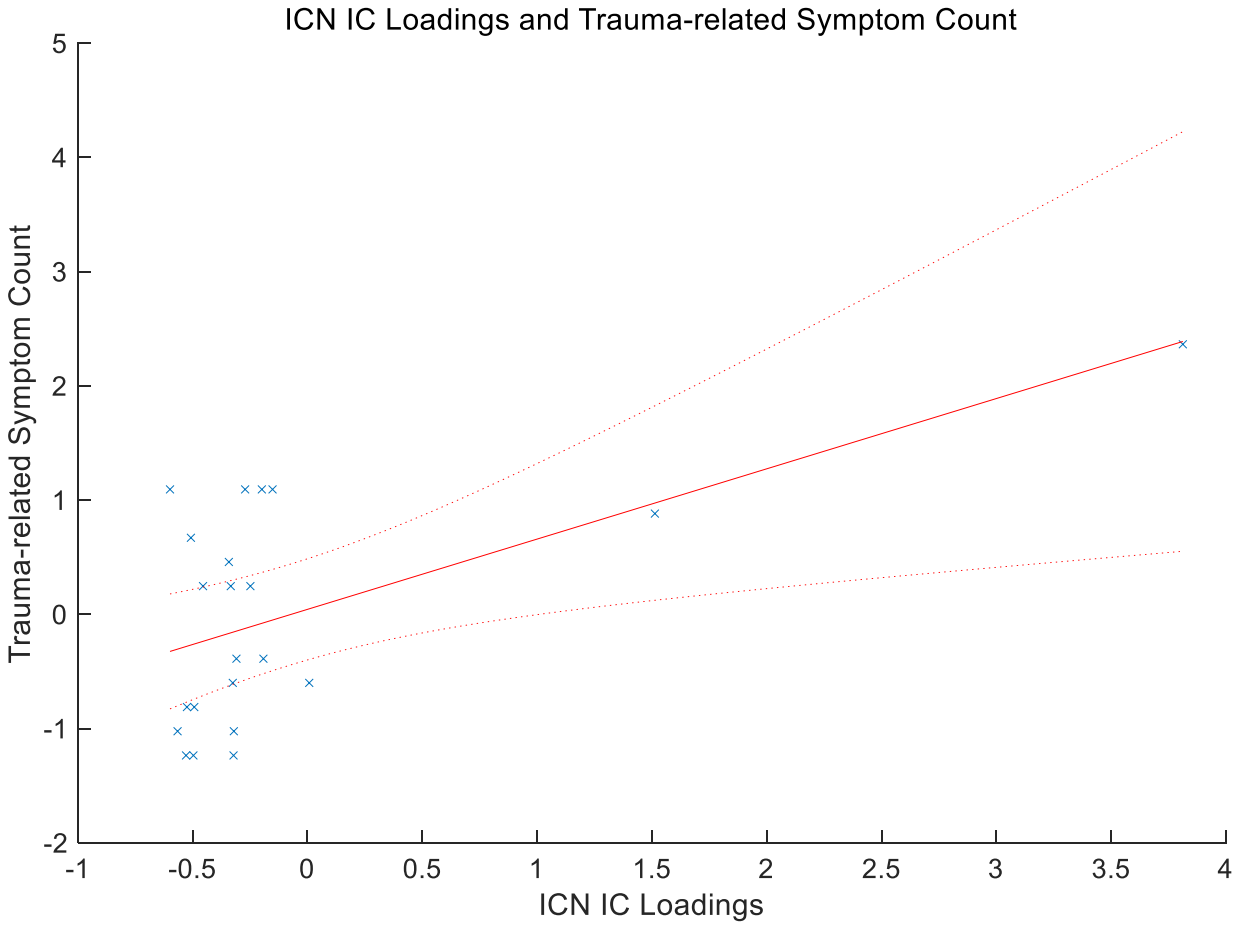

Figure 5. A robust regression model using subjects' intrinsic connectivity network independent component loadings to predict trauma-related symptom count. Outliers included.

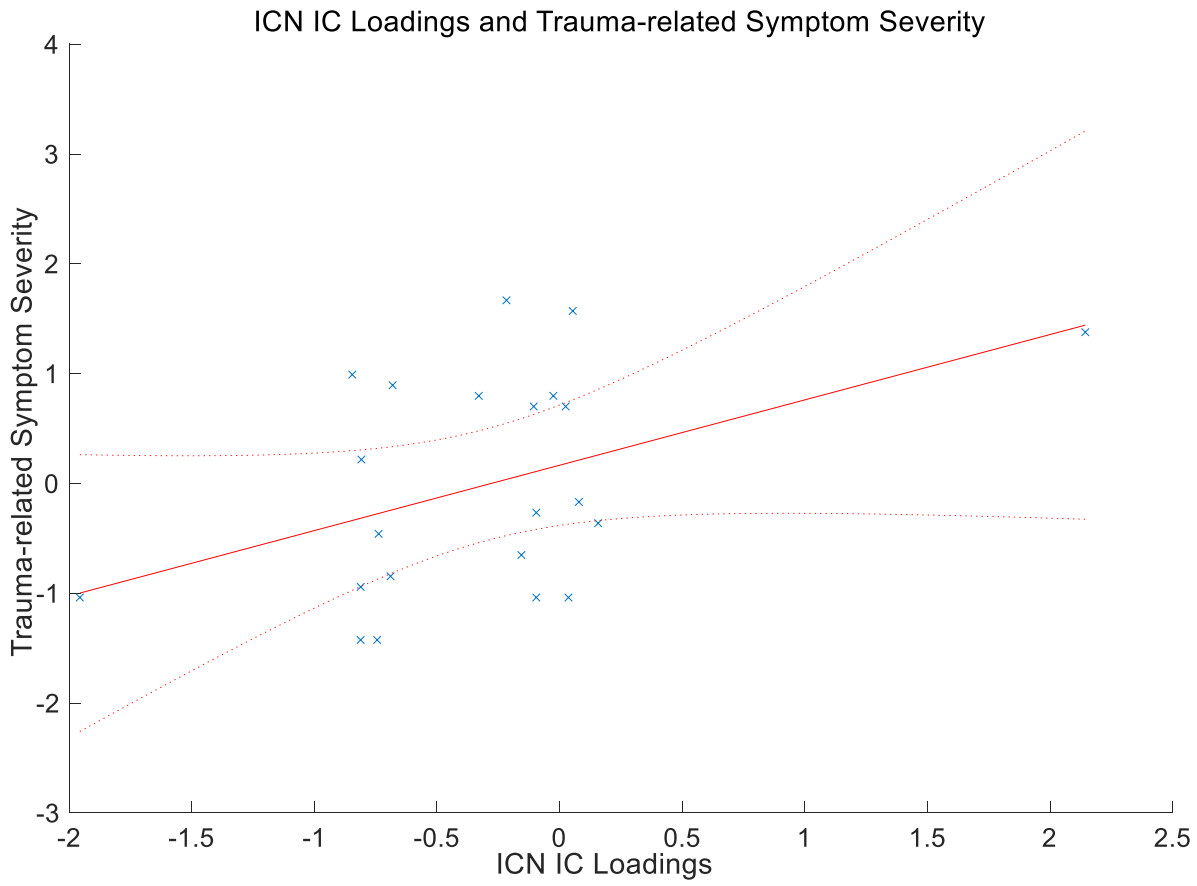

Figure 6. A robust regression model using subjects' intrinsic connectivity network independent component loadings to predict trauma-related symptom severity. Outliers included.

Table 6.

Robust regression results for white matter integrity ICs and trauma-related symptom count

Predictor	ß estimate	*t*-statistic	*p*-value
FA IC 1	0.34	1.3	0.205
FA IC 2	0.62	2.24	0.038

Robust regression results for white matter integrity ICs and trauma-related symptom severity

Predictor	ß estimate	*t*-statistic	*p*-value
FA IC 1	-0.00	-0.02	0.986
FA IC 2	0.41	1.44	0.167

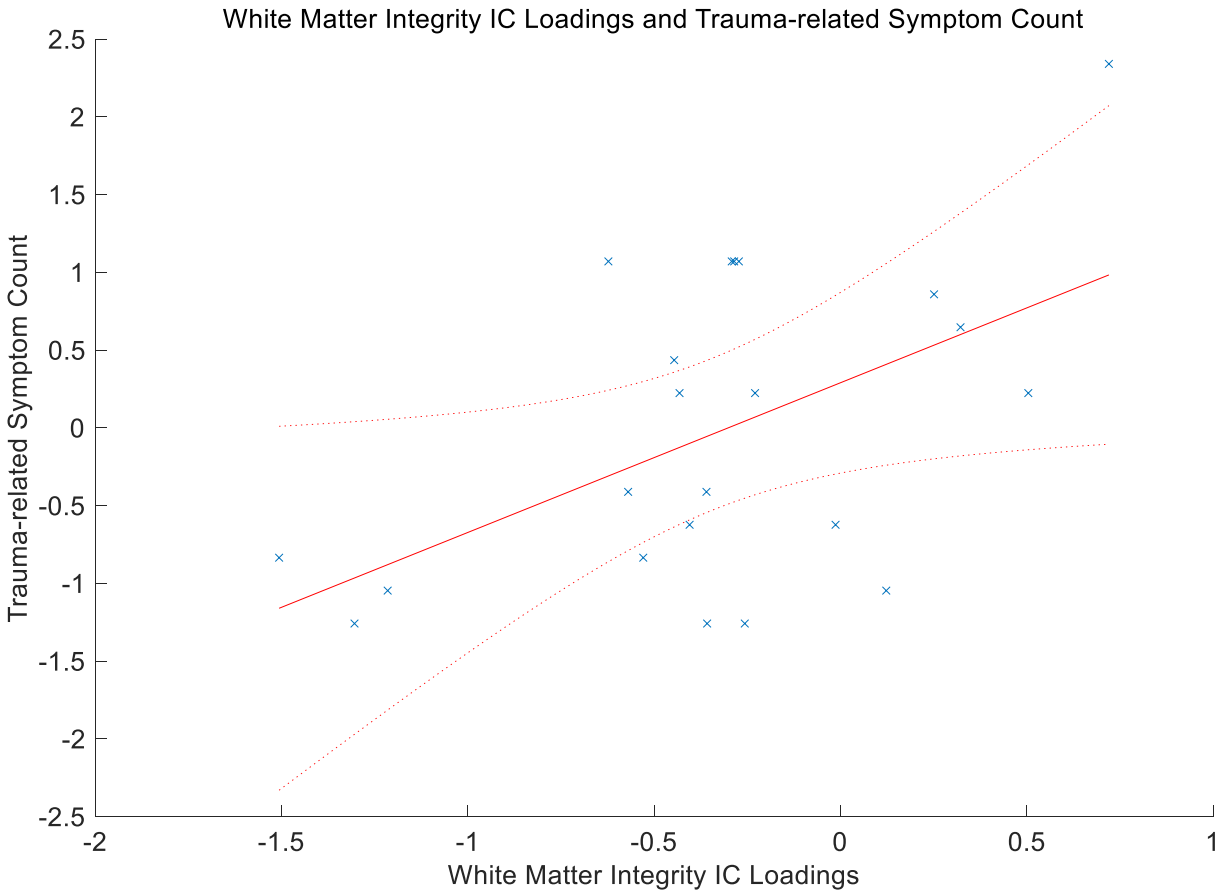

Figure 7. A robust regression model using subjects' whole brain white matter integrity independent component loadings to predict trauma-related symptom count.

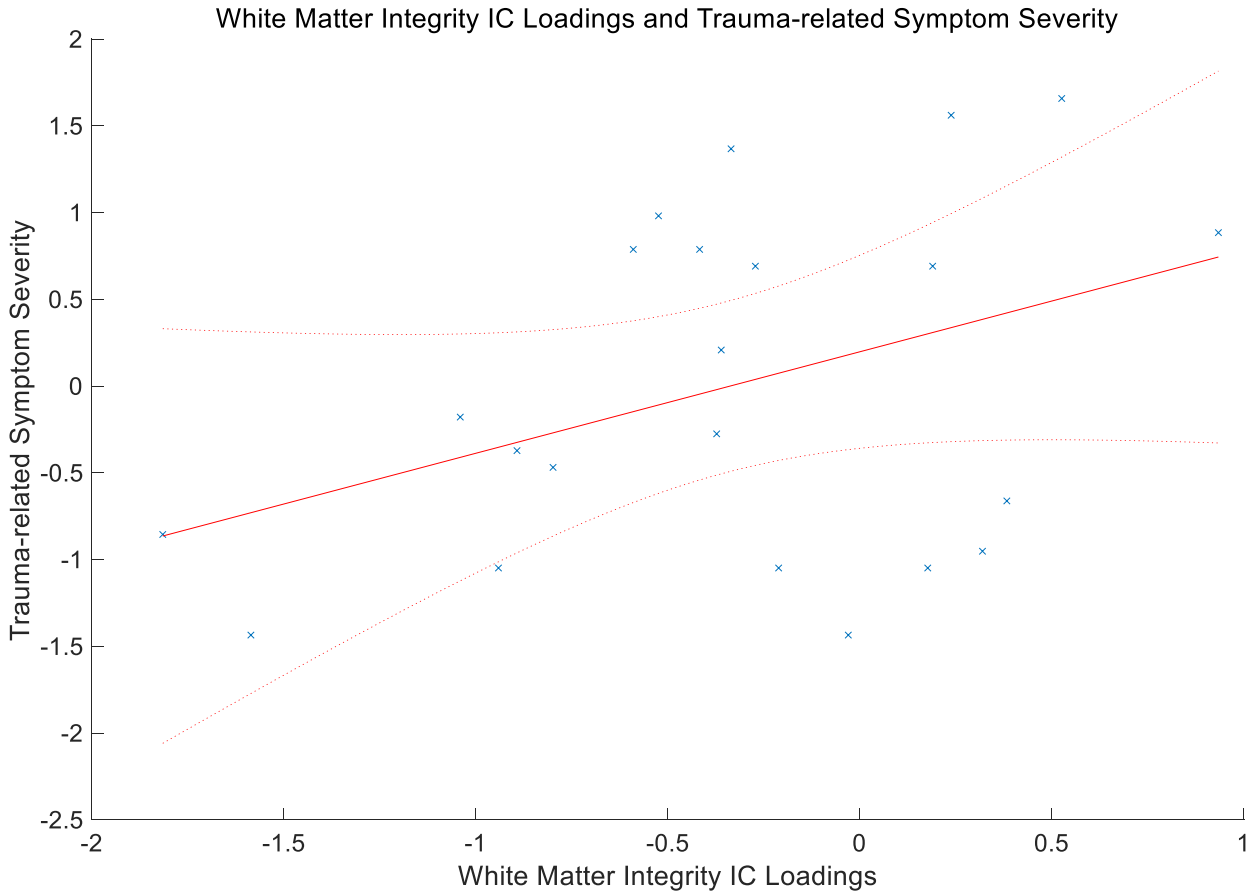

Figure 8. A robust regression model using subjects' whole brain white matter integrity independent component loadings to predict trauma-related symptom severity.

4. Discussion

4.1 Component-symptom relationships

We used a multi-method approach in an attempt to provide a more comprehensive and consistent interpretation of the interrelated structural and functional mechanisms that underlie trauma-related symptoms. Our aim was to test the relation between the connectivity of a fronto-limbic network, whole brain white matter integrity, and trauma-related symptoms in a non-clinical sample of trauma-exposed women. To accomplish this, we used pICA to decompose imaging data into ICs that vary jointly across participants. As a data-driven multivariate approach, pICA offers an advantage over more conventional univariate methods. As noted by

others, univariate region of interest (ROI) approaches assume that voxels or ROIs vary independently of one another, which is statistically stringent compared with the present approach (Meier et al., 2012). pICA does not assume each voxel within each modality to be independent, which decreases the number of assumptions made during analysis and increases discoverability. There is also evidence based on simulated data that the easing of assumptions in pICA does not lead to an increase in Type I errors (Meier et al., 2012).

There was a non-significant trend toward a greater number of trauma-related symptoms with increased subject loading onto fronto-limbic connectivity components. This trend was driven by a component which predominantly featured greater connectivity within subcallosal and orbitofrontal cortices. Given our small sample size, it should be noted that although this result was not statistically significant, the effect size is large. We selected this particular ICN because it is a fronto-limbic network composed of regions associated with the neurocircuitry model of PTSD, which suggests hyperactivity of the amygdala and hypoactivity of regions that exert top-down control over it, which includes the subgenual ACC and OFC (Patel et al., 2012). This model is supported by evidence that trauma exposure is related to decreased connectivity between the amygdala and prefrontal regions (e.g., Zhu et al., 2017). Follow-up ROI-based analyses are however necessary to meaningfully interpret how the trend level relationship found in our study may relate to previously reported differences in the connectivity between these regions and trauma-related symptoms.

There was a non-significant trend toward a greater number of trauma-related symptoms with increased subject loading onto the whole brain FA components. This trend was driven by a component that predominantly featured greater fractional anisotropy that overlaps with the forceps major and forceps minor tracts. Although this result was not statistically significant, it

reflects a medium effect size. The forceps major connects the occipital lobes via the splenium of the corpus callosum, and the forceps minor connects frontal cortices via the genu of the corpus callosum (Goldstein et al., 2017). There is evidence for greater white matter integrity in the forceps major (Li et al., 2016) and less white matter integrity in the forceps minor in trauma-exposed people with PTSD compared to trauma-exposed people without PTSD (Hu et al., 2016; Olson et al., 2017). Differences in white matter integrity as indexed by FA may relate to use-dependent myelin alteration caused by increased astrocyte activity (Ishibashi et al., 2006); however, there are other mechanisms that FA has been proposed to reflect. Exclusive use of voxel-wise comparison of FA values can also lead to misleading conclusions that reflect multiple tracts crossing within the same voxel (de Erausquin et al., 2013). Although our trend level FA results are in line with those of others (Li et al., 2016), further tractography-based analyses would be beneficial towards further characterization of the white matter integrity along the entirety of the forceps major and forceps minor tracts.

Whereas the components extracted by the pICA were not significantly correlated in our study, other groups have used pICA to extract correlated components across modalities (e.g., Gupta et al., 2015). Our approach shares commonalities with a previous study, specifically the use of FA to measure white matter integrity and the use of a minimum description length algorithm to estimate the number of ICs to be extracted during the pICA. Previously, pICA was used to extract ICs across data types that varied jointly across participants, however this was accomplished with a greater sample size (Gupta et al., 2015).

4.2 Limitations and future directions

Our study has a number of limitations and should be considered exploratory. First, whereas our study aimed to increase the discovery of relations across neuroimaging modalities

and trauma-related symptoms, our sample size was small. This small sample size limits interpretation, particularly in light of the presence of outliers in the subjects' ICN loading coefficients. Our small sample size also precludes meaningful exploration of how the specific trauma experienced by participants may relate to differences in the connectivity of the fronto-limbic network and whole brain white matter integrity. There is evidence that the distinct type of stressor experienced by the person has a distinct effect on neurobiological outcome (McLaughlin et al., 2019), and given a larger sample size we would be able to make comparisons between women exposed to interpersonal trauma and women exposed to non-interpersonal trauma (e.g., natural disasters).

Additionally, interpretation is limited by the nature of the components themselves. For example, the components extracted from the whole brain FA maps represent tissue that only partially overlaps with the tracts reported. PICA provides a means to explore relationships within multi-modal datasets and seems best complemented by more fine-grained post hoc analyses when used to test hypotheses related to specific regional differences in white matter integrity and resting-state connectivity. In the case of trauma-related symptoms, and disorders related to affect in general, structures as complex as the ACC are typically parcellated into subregions such as the subgenual ACC, however the components we extracted include multiple clusters within subgenual cortex. This suggests that the extracted ICN components could be further parcellated to better characterize the connectivity between regions included in this fronto-limbic network.

Another limitation is that our participants consisted exclusively of trauma-exposed women with and without trauma-related symptoms. Evidence supports the existence of resilience and vulnerability factors toward the development of trauma-related symptoms (Bolsinger et al., 2018). Previous studies have used experimental designs that include participants with trauma

exposure and trauma-related symptoms, trauma exposure without trauma-related symptoms, and non-trauma-exposed controls. Given that the mechanisms that underlie trauma-related symptoms are our interest, as opposed to neurobiological markers associated with trauma exposure, the mechanisms that underlie trauma-related symptoms may be more evident when trauma-exposed women with symptoms are compared with non-trauma-exposed controls, as opposed to trauma-exposed women without symptoms. Future studies would ideally incorporate study designs that allow for these comparisons.

Finally, our study was cross-sectional, which excludes causal interpretations. This limitation prevents us from drawing certain conclusions in regard to how the pICA derived ICs relate to the trauma symptoms. It is unclear, for example, if trauma exposure and accompanying trauma-related symptoms cause changes to the white matter integrity of the forceps major and forceps minor, or if greater white matter integrity of these tracts somehow confers vulnerability to the development of trauma-related symptoms after exposure to traumatic events.

4.3 Summary and conclusion

Our goal was to test the relation between the connectivity of a fronto-limbic network, whole brain white matter integrity, and trauma-related symptoms. PICA produced structural and functional components that represent greater white matter integrity of the forceps major and forceps minor and greater connectivity of subgenual and orbitofrontal cortices within a fronto-limbic network with subject loading coefficients that predicted the number of trauma-related symptoms in participants at a non-significant trend level, however these ICs were not correlated across modalities.

Although the present study is limited and preliminary, data fusion may prove useful in the exploration of the association between trauma-related symptoms and the structure and

function of the brain. When applied to multi-modal datasets of sufficient size, data fusion methods represent a valuable means to efficiently explore inter-modal relationships and leverage information afforded across data. Given that the neurocircuitry model of PTSD is supported by structural and functional evidence, our approach allows for a more comprehensive characterization of the structural and functional mechanisms that underlie and jointly vary with trauma-related symptoms.

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