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Sexual trauma history is associated with reduced orbitofrontal network strength in substance-dependent women

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ABSTRACT

Aim: Substance use disorders (SUDs) are highly comorbid with post-traumatic stress disorder (PTSD). PTSD-SUD comorbidity is associated with greater functional impairments and relapse risk. Women with SUDs experience markedly higher rates of trauma and PTSD compared to men with SUDs, particularly due to sexual and domestic abuse. Despite the strong association between trauma exposure and SUDs, the neurobiological correlates are understudied, particularly among females with SUDs. However, there is indication of abnormal somatic and interoceptive processing in women with PTSD. The present study examines interoception-linked differences in intrinsic brain networks in a group of women with SUDs and varying histories of trauma exposure, some of whom have a current PTSD diagnosis.

Methods: Pre-intervention data were analyzed from a subset ($N = 43$) of women in SUD residential treatment recruited for a mindfulness-based intervention efficacy clinical trial. Participants diagnosed with PTSD ($n = 14$) or not ($n = 29$) performed a task which involved attending to the somatic and visceral sensations of the breathing cycle (interoception) while undergoing a functional MRI (fMRI) scan. FMRI analysis employed independent components analysis and dual regression. First, we assessed differences in functional connectivity of interoception-modulated functional networks among those with and without PTSD. Second, we tested associations between network strength and lifetime sexual violence exposure across all participants on networks that showed significant group differences.

Results: PTSD diagnosis was associated with reduced functional connectivity of an orbitofrontal network with the precuneus, mid-posterior insula, lateral prefrontal cortex and angular gyrus. OFC network strength was inversely associated with sexual violence exposure over-and-above the contribution of PTSD status alone.

Conclusions: Our findings provide a novel network-level account of brain activity associated with PTSD among women with SUDs, which may inform treatment response in this subpopulation.

1. Introduction

1.1. Interoceptive awareness is compromised in SUD, and is a functional resource for recovery

Interoception describes the process by which the nervous system transduces, integrates, and interprets visceral and somatic sensory signals (Khalsa et al., 2018). These signals provide temporally dynamic maps of the body's homeostatic and physiological milieu at both conscious and unconscious levels of awareness (Hassanpour et al., 2016) which convey information critical for adaptive behaviors (Poppa and Bechara, 2018). The various sources of interoceptive information (e.g., cardiovascular, respiratory, gastrointestinal, immunological, etc.) are conveyed to the Central Nervous System (CNS), where they become integrated in somatosensory and viscerosensory representation. The primary neurofunctional pathways associated with interoception include the c-fiber and spinothalamic afferents, vagal afferent fibers, and specific brainstem and thalamic nuclei, which project to the insula (Craig, 2002). The influence of top-down control is evident from the up-regulation of activity linked to interoceptive signal processing in CNS

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(e.g., especially sectors of the insula) when attention is explicitly directed at bodily sensations (Avery et al., 2014; Farb et al., 2013b; Farb et al., 2013a; Schulz, 2016) and down-regulation when attention is directed away from bodily sensations (Brooks et al., 2002).

There is presently growing interest in the role of interoception and (interoceptive dysfunction) in psychopathology (for a summary see the Biological Psychiatry consensus statement from the 2016 Interoception Summit (Khalsa et al., 2018)). Interoception may be an important factor in substance use disorder (SUD), and in recovery from addiction (Verdejo-Garcia et al., 2012). For instance, psychoactive drugs stimulate bodily sensations (e.g., via autonomic system stimulation) and these sensations may become part of the feelings sought by frequent users. Similarly, withdrawal is marked by aversive interoceptive signals (e.g., aching and nausea) which can drive motivation to use. Interoceptive signals contribute to drug craving (Avery et al., 2016) and to mood states (Harrison et al., 2009, 2015) which can also be triggers for drug use (Cheetham et al., 2010; Shiffman, 2005). A chronic use history with a particular drug may alter the response to interoceptive signals, particularly when those signals are directly linked to the rewarding drug. For example, sympathetic arousal accompanying danger may normally provoke caution, but may provoke approach behavior in a cocaine-dependent individual, since the interoceptive signals of sympathetic activation are similar to those accompanying acute cocaine intake. In addition, impairment (or neglect) of interoceptive information could diminish the capacity for insight regarding problem drug use (Goldstein et al., 2009). Interestingly, alexithymia, the inability to recognize one's own emotional states, is associated with interoceptive deficits (Brewer et al., 2016; Hogeveen et al., 2016) and is frequently comorbid with SUD (Dorard et al., 2008). Alexithymia also predicts poorer long-term outcomes in treatment for SUD (Loas et al., 1997), suggesting the possibility that the interoceptive signals informing emotional awareness might be important resources for addiction recovery. Indeed several models of addiction treatment, including Cognitive Behavioral Therapy (CBT) and mindfulness-based interventions (Amaro et al., 2014) explicitly work with clients to help them better recognize their own bodily sensations. For example, in CBT, clients are taught to work to monitor their body for sensations of craving and to, “pay attention to all the somatic and affective signals and try to put them into words. What is the feeling like? Where is it?” (Carroll, 1998, pg. 51).

1.2. Impaired interoceptive awareness is a symptom of PTSD

If interoception is an important factor in SUD and recovery from SUD, then it is important to consider the implication for the significant subset of SUD individuals with co-morbid Post-Traumatic Stress Disorder (PTSD). Bodily attention appears to be relevant to the pathology of trauma-linked disorders, which includes intrusive memories and cognitions that may involve, or be triggered by interoceptive sensations and bodily awareness (Borgmann et al., 2014; Jung and Steil, 2013; Price, 2007; Smith-Marek et al., 2018). In line with these behavioral observations, PTSD and sexual trauma have previously been associated with altered brain metabolism in regions associated with interoceptive and somatosensory processing. Specifically, women with PTSD due to intimate partner violence have blunted subjective pain and pain-linked anterior insula responses that are inversely correlated with avoidant symptoms (Strigo et al., 2010), and (primarily) female patients with dissociative PTSD show reduced functional connectivity of vestibular brainstem nuclei with a parieto-posterior insula network and the dorsolateral prefrontal cortex (DLFPC) (Harricharan et al., 2017).

1.3. Trauma and substance abuse comorbidity

Exposure to traumatic events are as high as 93% in some SUD samples (Reynolds et al., 2011). Among substance dependent groups, the lifetime prevalence of PTSD has been estimated to be between 26% and 52%, with current prevalence between 15% and 42% (Vujanovic et al., 2016), depending on the sample. Women with SUDs experience markedly higher rates of traumatic stress and victimization compared to men with SUDs, particularly for traumas relating to childhood and adulthood sexual and physical abuse (Daigre et al., 2015; Fernandez-Montalvo, et al., 2015; Schäfer et al., 2010). Women with SUDs may also experience higher rates of current and lifetime PTSD compared to men with SUDs (Hyman et al., 2007; Reynolds et al., 2011). PTSD symptoms exacerbate (Hien et al., 2009; Ouimette et al., 2007) and are exacerbated by the presence of an SUD (Jacobsen et al., 2001). Individuals with co-occurring SUD and PTSD may face worse clinical outcomes, including greater psychosocial problems, need for services, more severe substance use, and higher rates of relapse than for individuals with SUD-only (Ouimette et al., 1998; Rosen et al., 2002).

Despite the established clinical relationship, trauma comorbidity in SUD is understudied in the neuroimaging literature. The few existing studies (notably: Regier et al. (2016); and Gawrysiak et al. (2017)) highlight heightened limbic drug-cue reactivity and enhanced amygdala-striatal resting-state functional connectivity, respectively, in cocaine-dependent men with histories of trauma. These findings suggest that there may be distinctive correlates of traumatic stress and brain function among individuals with SUD. However, neither study included participants with PTSD diagnoses, a clinically relevant distinction, since exposure to trauma-categoric events in absence of post-traumatic stress symptoms may not have the same effect on brain function, nor the course and outcome of a SUD. It remains the case that PTSD has, to our knowledge, not yet been evaluated in a neuroimaging study of a substance-dependent population. Given that women with SUDs experience markedly higher rates of trauma and PTSD relative to men with SUDs, especially due to interpersonal and domestic violence, there is a clear need to investigate neurobiological correlates in trauma-exposed, substance-dependent women with-and-without current PTSD diagnoses, as it may reveal functional differences with clinical implications.

The primary goal of the present report is to characterize deficits in interoceptive processing associated with PTSD comorbidity in a sample of women with SUD. To do this, we capitalize on the robust “attentional spotlight” effect, by which brain network activity supporting interoception is enhanced when attention is explicitly directed at bodily sensations (Brefczynski and Deyoe, 1999; Johansen-Berg et al., 2000). This allows us to evaluate whether comorbid PTSD is associated with anomalous BOLD response during an interoceptive challenge (attention to bodily sensations of breathing) and to characterize the nature of any observed anomaly at the level of brain functional networks. We study this issue in low socioeconomic-status (SES) women who recently completed detoxification and enrolled in a residential treatment program for SUDs. FMRI data were acquired during the baseline period (pre-randomization) from a subset of patients participating in a clinical trial of Moment-by-Moment in Women's Recovery (MMWR). MMWR is a trauma-informed, mindfulness-based adjunct intervention for low-income, ethnically and racially diverse women in residential treatment for SUDs (Amaro and Black, 2017). If interoception is indeed a critical factor in SUD and SUD treatment response, and if interoception is compromised among those with comorbid PTSD, then characterizing that compromise is an important step towards developing tailored treatment approaches for this subgroup.

We took a data-driven analytic approach, utilizing group independent components analysis and dual regression to identify task-modulated intrinsic functional networks that may distinguish female SUD patients with and without PTSD co-morbidity. We hypothesized that PTSD comorbidity will be associated with reduced integration of the insula within networks associated with interoceptive attention. Additionally, post-hoc correlational analyses of independent component networks that demonstrate significant spatial differences between the two groups were carried out to assess their association with lifetime exposure to sexual trauma across all participants.

2. Methods

2.1. Participants

The full sample of participants were 48 ethnically-diverse, socio-economically disadvantaged female patients initiating women-only residential treatment for polysubstance use disorders (primarily moderate-to-severe methamphetamine and/or cocaine use disorders). Inclusion criteria for the study were as follows: female, between 18 and 50 years old, diagnosed with SUD, fluent in English, right-handed, and a current patient in the residential treatment program partnered with the parent study. Exclusion criteria included contraindications for fMRI: currently or possibly pregnant, using medical devices (cardiac pacemaker, implanted cardiac defibrillator, etc.), metal fragments including shrapnel or other nonremovable metal devices including dental braces or retainers, intrauterine device, history of head trauma resulting in loss of consciousness for > 5 min, documented or subjectively reported claustrophobia, hair extensions or a wig connected by wire, permanent eyeliner, and BMI > 36. Additionally, participants were excluded from the parent study if they had an untreated severe chronic mental health condition or untreated psychotic disorder based on clinical intake LR-DSM-IV or DSM-V or diagnostic assessment, or reported suicidality during the prior 30 days based on clinical intake assessment.

Psychiatric diagnoses were based on LR-DSM-IV or DSM-V which were conducted by staff of the residential treatment program (the residential treatment program transitioned from the LR-DSM-IV to the DSM-V during the course of the clinical trial). Diagnoses were carried out by treatment center staff and confirmed by consensus meeting with the lead psychiatrist. Although comorbid psychiatric diagnoses were not exclusionary for the parent study, for the present analysis we excluded individuals with the following diagnoses: schizophrenia, anxiety disorder other than PTSD, no history of stimulant use (the majority of patients had primarily diagnoses of stimulant use disorders or had polysubstance use histories that included stimulants). Four participants were omitted based on these criteria. A large proportion of participants for whom information was available were taking prescribed psychoactive medications (39.5%) and/or had mood disorders (23.3%), therefore we did not exclude participants on the basis of medication use or mood-disorder status. One participant was removed from the study for the presence of non-removable dental work that the participant did not report during screening which caused signal dropout. The 43 remaining participants were included in the study, 14 of whom had received a PTSD diagnosis. Each of the 43 participants contributed two runs of fMRI data, except for four subjects (two from the PTSD, two from the noPTSD group) who contributed one run due to excessive motion (> 3 mm). See Table 1 for demographics and clinical characteristics. All study procedures were approved by the University of Southern California Institutional Review Board. Participants provided written informed consent and were compensated for their time.

2.2. Measures

2.2.1. Life stressors checklist – revised

The Life Stressor Checklist-Revised (LSC-R; Wolfe and Kimerling, 1997) is a measure of traumatic events and stressors that are particularly relevant to women's life experiences. Its use has been validated in women with co-morbid substance abuse and mental disorders, with histories of interpersonal violence victimization (McHugo et al., 2005). LSC-R follows a yes/no response format with follow-up questions that characterize the life stage(s) at which events occurred and the degree to which the respondent is currently affected by the experience. Events can be brief, single incidents or repeated traumas that may have occurred at any point in the lifespan (prior to age eighteen, adulthood, and within the last 8 months of the interview). For the present study, we use dichotomously scored responses (range: 0–30) reflecting events at any point during the lifespan.

2.2.2. Addiction severity index

Alcohol and substance use severity for the 30 days prior to treatment entry was assessed using the Addiction Severity Index (ASI: McLellan et al., 1992) and the Timeline Followback Interview (TLFB; Robinson et al., 2012).

2.2.3. Post-traumatic stress disorder (PTSD) symptoms scale

The PTSD Symptom Scale (PSS-I; Foa et al., 2005; Foa et al., 2018) is a semi-structured interview, which was used to obtain an overall severity score of PTSD symptoms according to DSM-IV, as well as separate severity scores for symptom subdomains: re-experiencing, avoidance, arousal. Scores range from 0 to 34, with higher scores reflecting more severe symptomatology.

2.3. The interoceptive-exteroceptive attention task

The Interoceptive-Exteroceptive Attention task (The IN-OUT task) was adapted from (Farb et al., 2013b), which investigated BOLD changes in interoceptive attention in response to Mindfulness-Based Stress Reduction (MBSR) training. The approach contrasts brain activity during attention to the sensations of breathing versus attention to an external target. By contrasting internally and externally directed focus, this approach capitalizes on the “attentional spotlight” effect, whereby

Table 1
Demographic and clinical characteristics of the study sample.

	All participants	SUD	SUD + PTSD	Test statistic	*P*-value
N	43	29	14		
Age	30.37 (7.7)	29.2 (8.4)	32.9 (5.6)	$t(41) = 1.5$	0.14
Ethnicity				$\chi^2(2) = 0.14$	0.93
Hispanic/Latina	65.1%	65.5%	64.3%		
Non-Hispanic Black	16.3%	17.24%	14.3%		
Non-Hispanic White	18.6%	17.24%	21.4%		
Other	0%				
Education				$\chi^2(2) = 3.6$	0.16
Less than HS degree	53.5%	51.7%	57.1%		
HS degree	32.6%	27.6%	42.9%		
Some college	13.9%	20.7%	0%		
ASI drug use	0.18 (0.15)	0.17 (0.14)	0.21 (0.18)	$t(41) = 0.74$	0.47
ASI alcohol use	0.11 (0.17)	0.095 (0.15)	0.13 (0.2)	$t(41) = 0.62$	0.54
Borderline diagnosis	16.3%	17.2%	14.3%	$\chi^2(1) = 0.06$	0.81
Mood disorder diagnosis	23.3%	24.1%	21.4%	$\chi^2(1) = 0.04$	0.84
Psychoactive medication	39.5%	41.4%	35,7%	$\chi^2(1) = 0.13$	0.72

ASI, Addiction Severity Index Drug and Alcohol use; HS, High School; values in first three columns refer to means with standard deviations in parentheses, otherwise percentages.

focus on a sensory quality amplifies the signal within brain regions associated with processing that sensory modality (Brefczynski and Deyoe, 1999; Johansen-Berg et al., 2000). Variations on this task have previously been used to isolate BOLD responses in regions associated with interoception in expert meditators (Hölzel et al., 2007), healthy individuals (Kuehn et al., 2016), as well as in clinical populations with depression (Avery et al., 2014) and anorexia nervosa (Kerr et al., 2015; Kerr et al., 2017). The magnitude of insula response during focused breathing tasks appears to track the quality of internal focus, which increases as a function of hours practiced in novices who participated in a mindfulness-based stress reduction (MBSR) program (Farb et al., 2013b). During the IN-OUT task participants performed two experimental conditions involving sustained attentional targets: the interoceptive (IN) condition and the exteroceptive (OUT) condition. Participants completed two runs, each containing nine blocks. The blocks were presented in pseudorandomized order- half of the runs contained five blocks of IN, and four blocks of OUT, while other blocks contained four blocks of IN and five blocks of OUT. For the IN condition, subjects were instructed to attend to bodily sensations associated with their breathing cycle with the following instructions: "*Please pay attention to the physical sensation of the breath wherever you feel it most strongly in the body. Follow the natural and spontaneous movement of the breath, not trying to change it in any way. Just pay attention to it. If you find that your attention has wandered to something else, gently but firmly bring it back to the physical sensations of the breath in the body*". During the IN condition, an "O" appeared on the center of the screen for 36 s, on which subjects were instructed to fix their gaze while simultaneously attending to the sensations of their breathing cycle. The OUT condition consisted of a "1-back" task, which we considered to be an attention control condition. During the OUT blocks, a letter from the set (A, B, C, D) was presented for 500 ms in a pseudorandom sequence. A fixation cross was presented in between each letter for 900 ms. When a letter repeated, the participant was instructed to press a key on the button box. The OUT blocks lasted 38.7 s. The sequence of letters presented, key presses, and response times were recorded for each OUT block. Prior to each block, the subject was presented with an instruction screen for 10 s that cued them to the upcoming block.

3. fMRI acquisition and analysis

3.1. Imaging set-up

Images were acquired with a 3 T Siemens MAGNETON Prisma System, with a 20-channel head coil. Functional images were obtained using a gradient echo, echo-planar, T2*-weighted pulse sequence (TR = 2000 ms, one shot per repetition, TE = 25 ms, flip angle = 90°, 64 × 64 in-plane resolution). Forty-one slices covering the entire brain were acquired with a voxel resolution of 3 cubic mm. Structural T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) images were acquired with the following parameters: TR = 1950 ms, TE = 2.26 ms, TI = 900 ms, Flip Angle = 7°, matrix = 256 × 224, 1 mm isotropic resolution, 176 sagittal slices, acquisition time = 241 s.

Respiration and pulse oximetry were measured during scanning using Biopac MP150 hardware and MR-compatible respiratory stretch transducer and pulse oximeter (Nonin Medical, 8600FO). Physiological data were sampled with a 1000 Hz sampling rate. The acquisition was synchronized to the scanner via a TTL pulse, and recorded in Biopac Acqknowledge software. The IN-OUT Attention task was scripted using MATLAB and Psychtoolbox 3.

3.2. fMRI pre-processing

RETROICOR (Glover et al., 2000) and respiratory and cardiac response functions (RVHRCOR; Birn et al., 2008; Chang et al., 2009) were applied to the functional volumes to reduce non-neuronal contributions of physiological noise. RETROICOR models periodic pulsatile noise in the BOLD time series associated with respiratory and cardiac cycles as a low-order Fourier phase expansion. RVHRCOR removes low-frequency cardiac and respiratory effects by convolving the respiratory and cardiac data with their respective response functions. The convolved cardiac and respiratory waveforms are then used as regressors for each voxel's time series using least squares. RETROICOR (order = 4) and RVHRCOR were performed in MATLAB using code obtained from C. Chang. Subsequent pre-processing steps were carried out in FSL (FMRIB's Software Library; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and included skull stripping with BET (Smith, 2002), motion correction (MCFLIRT; Jenkinson et al., 2002), slice-timing correction, high-pass temporal filtering (90 s), and spatial smoothing using a 5 mm Gaussian FWHM filter. Additional sources of movement and scanner noise were removed using FSL's MELODIC ICA for each individual run. Subject-level ICA-based denoising substantially improves the reproducibility of group-ICA decompositions relative to both motion scrubbing and nuisance regression (Pruim et al., 2015). Each component for each subject and run was manually inspected and labeled by an experimenter blind to participant diagnoses. Components flagged as artifact were regressed from the functional volume. The functional volumes were realigned to each participant's respective T1-weighted anatomical image, then normalized into standard space using 12°-of-freedom affine transformation and 2 mm resolution.

3.3. Group independent components analysis

To identify group-level intrinsic functional networks, we utilized the Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC; Beckmann and Smith, 2004) algorithm in FSL. Independent components analysis separates underlying sources from a linearly mixed multivariate signal. Preprocessed fMRI data from each subject and run were temporally concatenated into a single 4D file (each subject provided two runs of data, less the four subjects who provided only one run, for a total of 82 runs) and submitted to MELODIC analysis, with variance normalization. Thus, the group ICA solution reflects the combined contributions of both the PTSD and noPTSD groups. The dimensionality of the solution was constrained to 20 networks, a level of granularity commonly used to identify large-scale networks (Smith et al., 2009). Thereafter, the 20 group-level normalized networks were spatially cross-correlated against Smith et al.'s (2009) 20 network solution to determine their correspondence to a canonical set of intrinsic networks and artifacts.

3.4. Dual regression to obtain subject-level networks

In the first stage of the dual regression (Beckmann et al., 2009; Nickerson et al., 2017), the unthresholded group-level networks are first regressed onto each participant's fMRI series to extract beta-weights that form a subject-specific time series for each component and functional run (the spatial regression). Next, the variance-normalized time series for each component and run obtained from the first stage are used as predictor vectors for each participant's fMRI series to obtain a subject-specific component map (the temporal regression). These whole-brain spatial maps reflect each voxel's correlation with the group-level network; consequently, functional connectivity of a given network can manifest in any region of the brain, regardless of whether that region is typically associated with the canonical network. This approach allows identification of group differences in spatial connectivity of functional networks. We carried out dual regression on each group-level network individually, excluding: 1) the six networks deemed artifactual based on visual inspection and comparison with canonical networks and 2) the six networks that were not found to be significantly task-related (see Section 3.6 below). Thus, we carried out eight separate dual regressions on the networks identified as significantly associated with IN and OUT conditions of the task. Each dual regression produced two spatial maps per subject (corresponding to the

two runs, less the four exceptions who contributed one run of data). Each subject's *Z*-transformed maps were then averaged using the *fslmaths* to form a single 3D file for each component. These averaged subject-specific spatial maps for a given component were then concatenated to form a 4D file, which served as the input for cross-subject statistics.

3.5. Identification of task-modulated networks

To identify task-modulated networks in ICA-analysis of task fMRI data, we regressed the run-specific activity time courses for each network against the run's respective task-design matrix using the *fsl_glm* utility. This approach essentially answers the question of whether a network is more active in one task condition, by allowing us to determine the fit between the network time-course and task design for each run (Clewett et al., 2014; Wang et al., 2018). After combining the beta estimates and variance from each regression using a fixed effects approach to obtain a single parameter estimate per subject and component, we could determine which components were relatively more active during IN blocks compared to OUT blocks and visa-versa using one-sample *t*-tests. Since contrast estimates for the relative comparison of the two conditions (i.e. OUT > IN, IN > OUT) differ only in sign, *t*-tests were set-up such that positive values indicated the degree to which the network was relatively more active during the IN condition, while negative values indicated the degree to which the network was relatively more active during the OUT condition. The *p*-values were further Bonferroni corrected, which limited the number of networks only to those that most strongly differentiated the two task conditions. Components which were significantly associated with the task were used to compare spatial differences in network functional connectivity across the PTSD and noPTSD groups.

3.6. Functional connectivity of task-modulated networks

Group differences between noPTSD and PTSD were assessed for the networks that were determined to be significantly task-modulated, constrained to voxels within a binarized mask containing positive values. We used non-parametric Monte-Carlo based permutation testing with 10,000 permutations and alpha = 0.05 (Winkler et al., 2014). Clusters of activation were estimated using threshold-free cluster enhancement (TFCE) with a variance smoothing factor of 5 mm (Smith and Nichols, 2009). This procedure corrects for the family-wise error rate. Mean-centered age and ASI drug use severity scores were included as covariates of no-interest. Statistical maps were rendered onto a standard MNI brain using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). Probabilistic anatomical labels for cluster maxima were obtained from the Harvard-Oxford Cortical and Subcortical atlases, reported in standard MNI space.

4. Results

4.1. Demographic and clinical comparisons

Compared to those without a PTSD diagnosis, those with a PTSD diagnosis scored significantly higher on total PSS-I symptom severity ($t(41) = 2.01$, $p = .025$), and the subscales re-experiencing ($t(41) = 2.0$, $p = .025$) and avoidance severity ($t(41) = 1.9$, $p = .032$). However, compared to those with no PTSD diagnosis, those with a PTSD diagnosis did not exhibit higher scores on arousal symptoms ($t(41) = 1.26$, $p = .108$).

Apart from PTSD symptoms, the two groups did not differ on other clinical characteristics including current psychiatric medication use, other current co-occurring diagnoses, and ASI drug and alcohol use severity over the 30 days prior to intake. The PTSD group was slightly older on average (3.7 years), but the difference was not significant. Groups also did not differ on educational achievement. Statistics for these comparisons are presented in Table 1.

4.2. Lifetime trauma exposure

4.2.1. Life stressors checklist revised (LSC-R)

Participants in the study experienced varying exposure to traumatic events during childhood and/or adulthood such as death or incarceration of close relatives, criminal justice and/or child welfare involvement, homelessness, and victimization through domestic violence, sexual/physical assaults, emotional abuse/neglect, and human trafficking. Across both groups, participants endorsed an average of 13.2 (SD: 5.5, range: 3–22) items from the LSC-R. The difference in total LSC-R between the groups was not significant ($t(41) = 1.3$, $p = .19$), indicating that within the sample, the number of stressors experienced was not strongly predictive of meeting PTSD criteria. There was a positive correlation between age and the number of life stressors experienced ($r(41) = 0.33$, $p = .03$). The number of sexual trauma categories endorsed over the lifetime (yes/no: verbal sexual harassment, molestation, rape, and sex in exchange for goods or money qualified by the statement “when you did not want to”) accounted for 65.6% of the variance in total LSC-R item endorsement ($r(41) = 0.81$). The association between LSC-R total and Sexual Violence is comparable for both groups (PTSD: $r(12) = 0.87$; noPTSD: $r(27) = 0.78$). Given that sexual abuse is particularly relevant to the development of psychiatric problems in women, including addiction (Burnette et al., 2008; Koenen and Widom, 2009; Kendler et al., 2000), and has been linked to somatosensory gray matter and functional interoceptive deficits (Heim et al., 2013; Strigo et al., 2010), lifetime exposure to Sexual Violence was carried forward as the variable of interest for post-hoc tests. The two groups did not significantly differ in the number of endorsed Sexual Violence categories ($t(41) = 1.5$, $p = .14$).

4.3. Group independent components analysis and cross-correlation with a canonical resting state network template

The 20 ICs were spatially cross-correlated with Smith's 20 network solution (2009) to determine their correspondence with a set of canonical ICA templates and establish labels for the networks. Our ICA components demonstrated high correspondence to the templates: the primary (medial occipital; $r = 0.80$), secondary (occipital pole; $r = 0.68$) and tertiary (lateral occipital; $r = 0.66$) visual networks; the default mode (DMN; $r = 0.50$); a secondary DMN (DMN 2; $r = 0.48$); sensorimotor network ($r = 0.66$); bilateral auditory/insula network ($r = 0.78$); right-lateralized fronto-parietal network ($r = 0.62$); left-lateralized fronto-parietal network ($r = 0.67$); an executive/salience network ($r = 0.48$); an orbitofrontal network (OFC; $r = 0.39$); and a bilateral frontoparietal network ($r = 0.59$). There was an additional visual network in our solution that correlated with the secondary visual network ($r = 0.46$). The orbitofrontal network was also correlated with the default mode network ($r = 0.29$). We further identified a bilateral medial temporal network that did not have a clear correspondence to any brain networks in the Smith templates, with peak values located along the hippocampus and amygdala. The remaining six networks were determined to be artifactual, containing noise relating white matter, ventricles, and head motion.

4.4. Identification of task-modulated intrinsic networks

Of the 14 intrinsic brain networks labeled via template matching, eight satisfied the criterion for task relevance. Specifically, these networks were significantly differentiated for IN relative to OUT blocks. Networks with significantly greater activation during IN relative to OUT blocks included: medial temporal ($t(42) = 7.44$, $p < .00001$), DMN ($t(42) = 8.5$, $p < .00001$), DMN 2 ($t(42) = 4.1$, $p = .0002$), OFC ($t(42) = 3.75$, $p = .00054$), and medial occipital ($t(42) = 5.4$, $p < .00001$). Networks with significantly greater activation during the

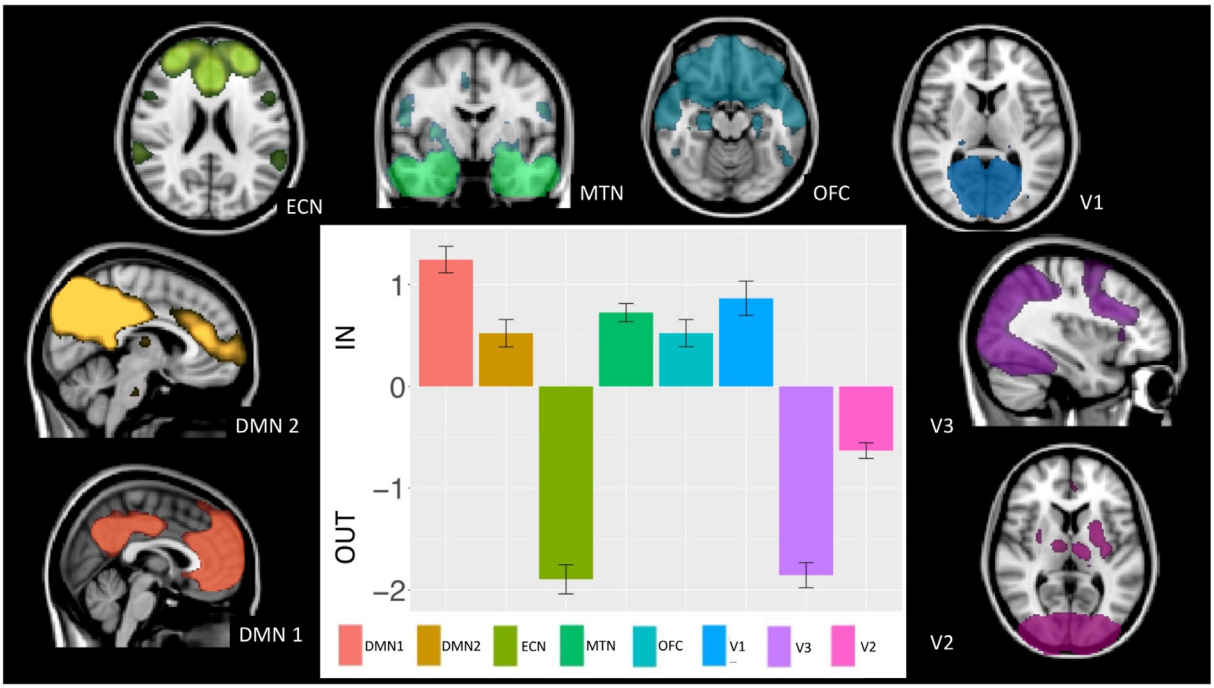

Fig. 1. Group-level ICA networks that were significantly task-modulated. Bar plots describe the beta weights for the fit between the subject level design matrix and their respective network time course. Negative values indicate the degree to which the network is more active during exteroceptive attention relative to interoceptive attention (OUT – IN), while positive values indicate the degree to which the network is more active during the interoceptive (IN) condition relative to the OUT condition (IN – OUT). DMN 1 = Default Mode network, DMN 2 = secondary Default mode network, ECN = Executive network, MTN = Medial temporal network, OFC = Orbitofrontal network, V1 = Medial occipital network, V3 = Lateral occipital network, V2 = Occipital pole network.

OUT relative to IN blocks included: executive ($t(42) = -13.5$, $p < .00001$), occipital pole ($t(42) = -5.7$, $p < .00001$), and lateral occipital ($t(42) = -6.0$, $p < .00001$. Accordingly, spatial differences in network functional connectivity for PTSD and noPTSD groups were tested on these eight networks. See Fig. 1.

4.5. Spatial differences in network functional connectivity for PTSD versus noPTSD

To infer group differences in functional connectivity for the eight task-modulated networks, we conducted non-parametric voxel-wise regressions using *randomise* in FSL. These tests included the one-tailed contrasts noPTSD > PTSD and PTSD > noPTSD for each network, controlling for recent drug use and age (demeaned across both groups) as covariates of no-interest. Given that there were two contrasts performed on each network, a total of 16 tests were carried out. Accordingly, the TFCE-corrected *p*-values for cluster significance were further Bonferroni-corrected, with the alpha criterion for significance adjusted to 0.05/16 = 0.003125.

Of the eight networks, only the orbitofrontal (OFC) network contained clusters that exceeded TFCE and Bonferroni-corrected thresholding for the test comparing spatial differences in functional connectivity for noPTSD > PTSD. Differences in OFC functional connectivity were located in the bilateral insula, postcentral gyrus, precuneus, lateral OFC/frontal operculum, and left frontoparietal areas. The OFC network result is displayed at the Bonferroni-corrected threshold in Fig. 2. MNI-coordinates for the peaks of clusters obtained from this analysis are reported in Table 2.

The PTSD group did not display greater functional connectivity in any brain region for any of the eight networks.

4.6. Mean OFC network strength associated with lifetime exposure to sexual trauma

Given that the majority of participants (62.8%) had experienced at least one LSC-R sexual trauma category at some point in their life regardless of PTSD diagnosis, and that sexual trauma accounted for a large portion of variance in total LSC-R, independent post-hoc tests were carried out to identify whether the average strength of each participant's OFC network was associated with lifetime exposure to Sexual Violence above and beyond the effects of PTSD status. A multiple linear regression was calculated to predict the whole-brain average of the subject-level variance-normalized networks (masked for positive voxel-values), based on PTSD status (PTSD = 1, noPTSD = 0), Sexual Violence total, age, ASI drug and alcohol use. For the OFC Network, a significant regression was found ($F(5, 37) = 5.34$, $p = .00086$, with adjusted-$R^2 = 0.34$. Age, alcohol and drug use were not significant predictors ($\beta = -0.02$, SE = 0.019, $p = .26$; $\beta = 0.28$, SE = 0.91, $p = .76$; $\beta = 0.78$, SE = 0.99, $p = .43$), whereas both PTSD and Sexual Violence independently explained significant variance: PTSD was associated with lower average OFC functional coherence ($\beta = -0.92$, SE = 0.30, $p = .0039$), consistent with the analysis of group differences in OFC network functional connectivity, while Sexual Violence accounted for additional variance ($\beta = -0.24$, SE = 0.095, $p = .015$), suggesting a cumulative effect of sexual traumas on the integrity of the OFC network across substance-dependent women both with and without PTSD (see Fig. 3). The model intercept was also significant ($\beta = 4.6$, SE = .58, $p = < .0001$). As a check on whether Sexual Violence accounts for similar variance as compared to total LSC-R score given the very high correlation between the variables (see Section 4.2.1), the same regression was run using total LSC-R score instead of Sexual Violence. In this model, LSC-R total was only a marginally significant predictor of OFC strength ($\beta = -0.055$, SE = 0.027, $p = .052$) whereas the estimates of the other predictors (PTSD, age, ASI drug and alcohol use) remained very similar.

5. Discussion

To our knowledge, this is the first study to investigate neural correlates of PTSD and traumatic stress in women diagnosed with SUD. To

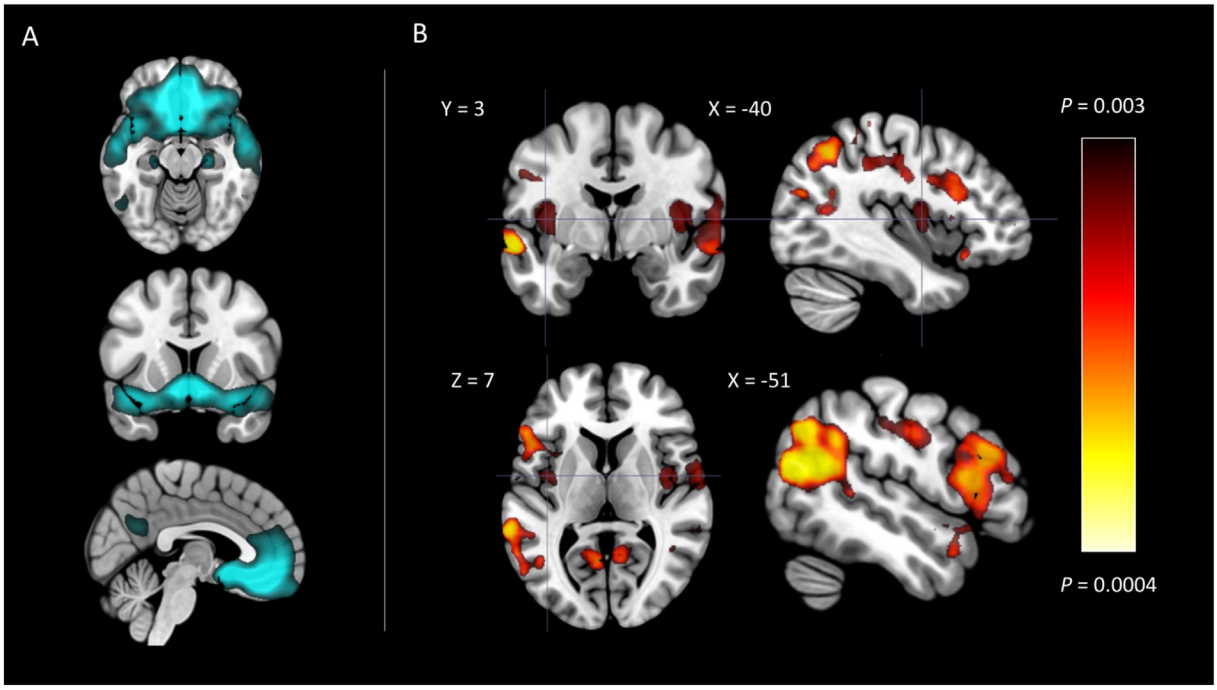

Fig. 2. (A) Group-level OFC network from the MELODIC analysis. (B) Group differences in functional integration of the OFC network. The group with PTSD exhibited reduced OFC network functional connectivity in multiple brain regions, including the bilateral mid-posterior insula, somatosensory cortex, precuneus, left middle and inferior frontal gryus, lateral occipital cortex/angular gyrus. Results displayed are TFCE and Bonferroni-corrected for multiple comparisons.

address the question of differences between trauma-exposed, substance-dependent women with and without current PTSD, we employed a data-driven approach. First, using independent components analysis and dual regression, we identified eight intrinsic functional networks that were significantly modulated by the interoceptive and exteroceptive task conditions. These eight task-modulated networks were used to test network-level differences in functional connectivity for participants with comorbid PTSD and SUD compared to those with SUD-only. Only the OFC network significantly differentiated the PTSD and noPTSD groups. Notably, we did not identify brain or performance differences (see Supplement) between PTSD and noPTSD for networks associated with exteroceptive task demands (the executive, lateral occipital, and occipital pole networks). Rather, group differences were found for the OFC network, whose time course was more active when participants were cued to attend to the sensations associated with their breathing cycle. Hence, group differences were specific to a brain network involved in attentional modulation of viscerosensory processing.

The OFC is a functionally heterogeneous multimodal sensory-motor association region. The lateral sector of the OFC is a convergence zone for sensory inputs from multiple modalities, including somatosensory and visceral afferents (Rolls, 2004) while the medial sector of the OFC provides outputs to brainstem visceromotor and hypothalamic structures (Ongur and Price, 2000). In general, the OFC is functionally and anatomically coupled with the insula, striatum, lateral prefrontal cortices, and limbic structures (Feldman Barrett and Simmons, 2015; Zald et al., 2014). In relation to complex behaviors, the OFC is integral to functional states related to homeostasis and allostasis, such as mood and emotion (Bechara et al., 2000; Zhang et al., 2016), hypothalamic-pituitary-adrenal-axis (HPA) activity (Sinclair et al., 2012), reward (Howard et al., 2015), and decision-making (Bechara and Damasio, 2005). Our observation of diminished OFC strength and functional connectivity in the PTSD group is highly consistent with many prior studies of post-traumatic stress in non-substance dependent individuals, who show reduced orbitofrontal or ventromedial prefrontal cortex (VMPFC) metabolism across a variety of task-demands, including trauma-related (Daigre et al., 2015; Moser et al., 2015) and trauma-unrelated task contexts (Felmingham et al., 2009; Herz et al., 2016; Rougemont-Bücking et al., 2011; Sripada et al., 2012; van Rooij et al., 2016). Confirming the association of PTSD with OFC/VMPFC function, a meta-analysis of 79 neuroimaging studies of PTSD also concluded that

Table 2
MNI coordinates of cluster peaks.

Peak Clusters noPTSD > PTSD	Hemisphere	Cluster Size (Voxels)	x	y	z
Lateral occipital cortex, Angular gyrus, Lateral orbitofrontal, Inferior frontal gyrus, Middle frontal gyrus, Pre-central gyrus, Post-central gyrus	L	8891	−54	−68	20
Central operculum, Post-central gyrus, Mid-posterior insula, Superior temporal gyrus, Posterior cingulate	R	3857	62	−12	−8
Precuneus, Lingual gyrus	L/R	2773	−14	−52	−2
Angular gyrus, Lateral occipital cortex, Middle temporal gyrus	R	882	60	−58	20
Mid-posterior insula	L	297	−36	−4	0
Supplementary motor cortex, Cingulate gyrus	L/R	124	10	−6	46
Lateral orbitofrontal cortex	R	57	46	22	−14
Frontal pole	L	11	−44	52	0
Anterior cingulate	L	6	−8	−2	42

All coordinates reported in MNI space. Peak cluster reported for a main cluster, but several maxima may be observed within a given cluster as large clusters were bridged by several voxels.

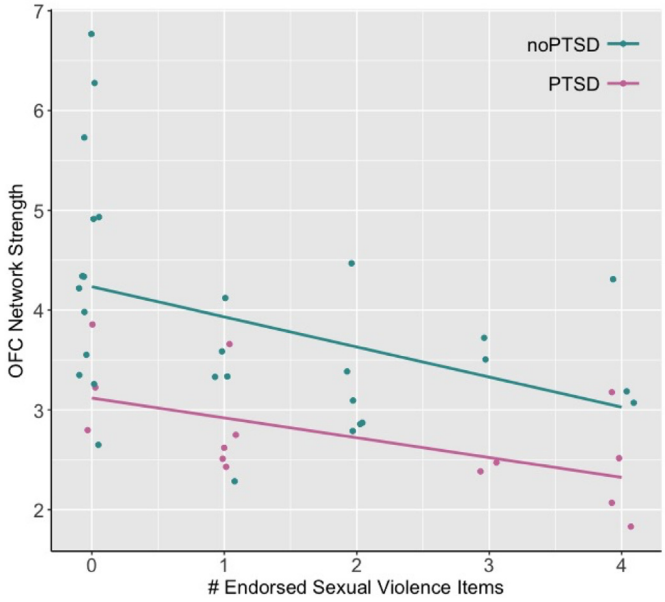

Fig. 3. Sexual Violence exposure and PTSD status are significantly negatively associated with mean OFC Network strength. Scatterplot reflects the simple correlation between Sexual Violence and OFC Network for each group.

PTSD is associated with hypoactivity of ventromedial prefrontal regions, as well as of the inferior frontal gyrus (Hayes et al., 2012).

The OFC is also a stress-sensitive cortical structure. Pre-clinical research has established that chronic stress exposure leads to dendritic atrophy of the medial and orbital OFC (Liston et al., 2006), and altered activity of forebrain glucocorticoid receptors, which are involved in feedback regulation of the HPA-axis (Arnsten, 2009; Boyle et al., 2006; Herman et al., 2012). It is repeatedly observed that adults and youth who experience childhood adversity have structural abnormalities of the OFC, expressed as reduced gray matter volumes (Hanson et al., 2010; Hart and Rubia, 2012). It is possible that depressed metabolism and volume of the OFC is a consequence of early experiences, which generate a vulnerability for the development of PTSD in response to traumas. Alternatively, OFC atrophy and hypometabolism could also reflect the neurobiological consequences of traumatic stress and PTSD itself. Suggestively, Morey et al. (2016) report that maltreated youth with PTSD have decreased VMPFC gray matter volume relative both to maltreated youth without PTSD and non-maltreated controls. More directly, Dahlgren and colleagues reported a twin study indicating that diminished medial prefrontal function is an acquired (rather than pre-existing) feature of PTSD (Dahlgren et al., 2018). Our data also suggest that diminished OFC network strength is predictive of current PTSD. We further observed that the strength of the OFC network for each subject was negatively associated with the severity of sexual trauma history across all participants, over-and-above the contribution of PTSD status alone. These results suggest that functional integrity of the OFC network is also sensitive to the cumulative effects of exposure to sexual trauma in women with SUD.

The spatial differences in orbitofrontal network connectivity manifested in a set of brain regions associated with interoception, somatosensation, bodily self-consciousness, and cognitive control. Concerning visceral and somatic sensation, the PTSD group demonstrated reduced bilateral mid-posterior insula and somatosensory cortex functional connectivity with the OFC network, which may suggest weaker interoceptive and somatic representations of the body and viscera during breath awareness. The mid-posterior insula is the terminus of major vagal and spinothalamic lamina I pathways that convey homeostatic and viscerosensory information to the cortex (Craig, 2002). Activity in this region is responsive to homeostatic states and interoceptive manipulations. According to one model, interoceptive information is propagated along a posterior-anterior axis in the insula, eventually reaching the orbitofrontal cortices, whereby visceral status can affect mood as well as goal-directed behaviors, including drug seeking (Naqvi and Bechara, 2010). Mindful or attentive breathing exercises can be seen as an interoceptive manipulation. Brief interventions that employ attention to breathing are known to transiently decrease subjective states of distress in both clinical and healthy populations (Brown et al., 2013; Johnson et al., 2015; Ng et al., 2016). In an fMRI paradigm, attention to breathing also downregulates amygdala responses and increases prefrontal activity during emotional picture viewing (Doll et al., 2016), which suggests a potential brain mechanism through which mindfulness practices may support emotion regulation. Activation of lateral prefrontal regions are also observed in fMRI studies of focused-meditation (Brefczynski-Lewis et al., 2007; Tomasino and Fabbro, 2016). In particular, Hasenkamp et al. (2012) reported that greater dorsolateral prefrontal activity was associated with periods of greater self-reported focus during such exercises, whereas it diminished during periods of mind-wandering and "awareness of" mindbwandering. These reports suggest that cognitive control is required to sustain attention on body sensations and inhibit mind-wandering. In our study we observed reduced OFC functional connectivity with the dorsal and ventrolateral prefrontal regions in the PTSD group relative to the noPTSD group. Furthermore, it is reported that in women with PTSD, low executive functioning is related to greater intrusive thought persistence and cognitive avoidance strategies (Bomyea and Lang, 2016). Initially, women with SUD-PTSD comorbidity may have more difficulties engaging the interoceptive and attentional resources that may support emotional regulation in the context of mindfulness practices, which could be relevant to understanding the efficacy of mindfulness-based interventions for this sub-population.

In addition to the insula, in the PTSD group we also observed reduced OFC functional connectivity with the angular gyrus/temporal-parietal junction (TPJ) and lateral occipital cortex (in particular, an area consistent with the extrastriate body area). These areas are involved in sensorimotor integration of vestibular, interoceptive, proprioceptive, motor, and visual inputs that support the sense of body ownership, agency, first-person perspective and localization in space (Blanke, 2012; Leménager et al., 2014; Suchan et al., 2013). Associative pairing of self to a visual symbol also activates these regions relative to associative pairing of visual symbols to non-self objects (Sui and Gu, 2017), and lesions of the extrastriate and temporo-parietal cortices can produce disorders of bodily self-consciousness (Anzellotti et al., 2011; Heydrich and Blanke, 2013), and these regions appear to be relevant to dissociative PTSD (Harricharan et al., 2017). TPJ activations have also been observed during breath awareness paradigms (Dickenson et al., 2013). Observed differences in functional connectivity of these regions with the OFC network during interoceptive attention is particularly interesting given that reduced medial OFC metabolism has previously been associated with dissociative symptoms in PTSD (Tursich et al., 2015).

5.1. *Stress regulation, interoceptive exposure and mindfulness for relapse prevention*

Stress increases the likelihood of relapse in individuals with histories of addiction (Blaine and Sinha, 2017; Sinha, 2008), an effect which may be more pronounced in females with SUDs (Maria et al., 2014). In the context of traumatic stress, drug use may serve as an avoidance or numbing strategy in response to aversive interoceptive and emotional states. Use-withdrawal-relapse cycles contribute to dysregulation of HPA, sympathetic-adrenal medullary (SAM) and immune response systems (Kubera et al., 2008; Michopoulos et al., 2016) which may worsen traumatic stress symptoms (Jacobsen et al., 2001). Mindfulness treatments tailored to women with comorbid substance abuse and traumatic stress may be especially suited for addressing

dysregulated stress responses that can precipitate relapse. Specifically, certain mindfulness exercises such as focused breathing and the body scan may act as a form of interoceptive exposure therapy, as well as serve to re-integrate an embodied sense of self, and down-regulate stress-reactivity. In healthy individuals, mindfulness training has been found to strengthen white matter connectivity between insula and the prefrontal cortex, including the OFC (Sharp et al., 2018). Moreover, part of mindfulness training consists of developing a metacognitive stance towards aversive physiological states, thoughts, and emotions, which may reduce dissociation and conditioned behaviors, including drug seeking, in response to interoceptive or psychological stressors (Amaro et al., 2014; Bowen et al., 2018; Boyd et al., 2018).

5.2. Limitations and future directions

First, our sample size is modest for group comparisons. However, we employed nonparametric permutation methods for inference of group differences, a statistically strict method which has been shown to generate minimal levels of false positives relative to parametric methods of inference (Eklund et al., 2016), and we applied Bonferroni correction on the tests performed, further reducing the potential for false positives. Moreover, the observation of depressed OFC network function and connectivity is highly consistent with prior studies. Nevertheless, the risk of Type 1 error related to "file-drawer problems" is heightened when sample sizes are small, as is the case in the present study, and so the results presented here should not be taken as definitive. Second, this study was cross-sectional, therefore the design does not allow us to distinguish whether group differences in brain metabolism are antecedent (and perhaps causal contributors) to the development of PTSD or whether these differences are related to the sequelae of PTSD (or the sequelae of PTSD in the context of addiction). Although psychoactive medication use was similar across the two groups, the potential influence of these medications could not be ruled out. We were also not able to exclude subjects on the basis of psychiatric comorbidities apart from PTSD. However, comorbidity in SUD is common, and in the present study the rates of mood and borderline disorders were similar between PTSD and noPTSD groups, thus these data may be more representative of female SUD populations, thereby supporting the generalizability of the findings. Nevertheless, it is not entirely clear how substance use may have interacted with the present findings (i.e. limiting its generalizability to PTSD specifically). OFC gray matter and functional impairments have also been noted in substance abuse disorders (Goldstein and Volkow, 2011; Tanabe et al., 2009). Similarly, interoceptive processing deficits have also been observed in substance dependent individuals without PTSD (May et al., 2013; Stewart et al., 2014). Consequently, it is not clear whether PTSD results in primary deficits in processing somato-visceral information relative to SUD, or whether this relative difference might be a consequence of a supraordinate factor such as attentional difficulties (although there were no performance differences in the exteroceptive task [see Supplement]). However, since we did not have a measure of performance difficulty for the two task conditions, we also cannot be certain whether perceived difficulty played a role. Behavioral measures of interoception should be incorporated in future studies, or, alternatively, could utilize assessments of interoceptive function that do not necessarily impose attentional or cognitive demands (e.g. pharmacological challenges). To address these interpretive ambiguities, future studies could incorporate demographically matched, non-substance abusing comparison groups with-and-without trauma/PTSD to identify associations of the OFC and interoceptive networks that are uniquely related to substance abuse versus those related to PTSD, and potential interactions between the disorders. Lastly, in the current study we only assessed participants at a single time-point, soon after admission to SUD treatment, thus we do not know how interoceptive, somatosensory and orbitofrontal function may change with treatment. However, we have identified that insula and orbitofrontal metabolism, as well as functional connectivity between these regions may be useful neurobiological marker of clinical response for women with PTSD and substance abuse disorders.

6. Conclusion

Interoception is increasingly recognized as a construct relevant to the symptomatology of mental health conditions, including substance abuse and anxiety disorders. As the first neuroimaging study to examine SUD and PTSD comorbidity in women with varying degrees of exposure to traumatic stressors, we provide a novel brain network-level account of interoceptive differences within this sub-population. Specifically, in the PTSD subgroup we observed reduced functional connectivity of an orbitofrontal network with the insula, somatosensory and cognitive control regions during an interoceptive task during which participants attended to sensations of breathing. Group differences in network functional connectivity were specific to task-modulated networks associated with interoception, and not those associated with exteroception. Post-hoc correlational analyses further identified a cumulative association between sexual trauma exposure and OFC network strength during interoception, independently from PTSD status. Traumatic stress-dependent differences in the orbitofrontal cortices may be relevant to the clinical responses to interventions for women with substance use disorders.

Declaration of Competing Interest

All authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101973.

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