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Amygdala functional connectivity in the acute aftermath of trauma prospectively predicts severity of posttraumatic stress symptoms

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ABSTRACT

Understanding neural mechanisms that confer risk for posttraumatic stress disorder (PTSD) is critical for earlier intervention, yet longitudinal work has been sparse. The amygdala is part of a core network consistently implicated in PTSD symptomology. Most neural models of PTSD have focused on the amygdala's interactions with the dorsal anterior cingulate cortex, ventromedial prefrontal cortex, and hippocampus. However, an increasing number of studies have linked PTSD symptoms to aberrations in amygdala functional connections with other brain regions involved in emotional information processing, self-referential processing, somatosensory processing, visual processing, and motor control. In the current study, trauma-exposed individuals (N = 54) recruited from the emergency department completed a resting state fMRI scan as well as a script-driven trauma recall fMRI task scan two-weeks post-trauma along with demographic, PTSD, and other clinical symptom questionnaires two-weeks and six-months post-trauma. We examined whether amygdala-whole brain functional connectivity (FC) during rest and task could predict six-month post-trauma PTSD symptoms. More negative amygdala-cerebellum and amygdala-postcentral gyrus FC during rest as well as more negative amygdala-postcentral gyrus and amygdala-midcingulate cortex during recall of the trauma memory predicted six-month post-trauma PTSD after controlling for scanner type. Follow-up multiple regression sensitivity analyses controlling for several other relevant predictors of PTSD symptoms, revealed that amygdala-cerebellum FC during rest and amygdala-postcentral gyrus FC during trauma recall were particularly robust predictors of six-month PTSD symptoms. The results extend cross-sectional studies implicating abnormal FC of the amygdala with other brain regions involved in somatosensory processing, motor control, and emotional information processing in PTSD, to the prospective prediction of risk for chronic PTSD. This work may contribute to earlier identification of at-risk individuals and elucidate potential intervention targets.

1. Introduction

Trauma exposure is common, with a recent national epidemiological study estimating that 90–94% of U.S. adults endorse having experienced a traumatic event (Kilpatrick et al., 2013) as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000, DSM-IV; American Psychiatric Association, 2013, DSM-5). While most trauma-exposed individuals are resilient, a significant portion (8–10%) will develop posttraumatic stress disorder (PTSD; Kilpatrick et al., 2013). Therefore, determining the neural mechanisms that confer PTSD susceptibility versus resilience is critical.

The amygdala is a core region implicated in PTSD. While other brain regions are also relevant to our understanding of PTSD symptomology, including the default mode network (medial prefrontal cortex, posterior cingulate cortex), salience network (insula, dorsal anterior cingulate

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cortex (dACC)), and frontoparietal network (dorsolateral prefrontal cortex, parietal cortex; e.g., Lanius et al., 2015), we chose to focus on the amygdala, given its prominent role in causal models of aberrant fear processing in PTSD. Several positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional neuroimaging (fMRI) studies have consistently demonstrated that individuals with PTSD show greater amygdala activation when viewing negative emotional faces (Bryant et al., 2008; Felingham et al., 2010; Fonzo et al., 2010; Killgore et al., 2014; Rauch et al., 2000; Shin et al., 2005; Stevens et al., 2013), negative emotional scenes (Brohawn et al., 2010; Patel et al., 2016; St. Jacques et al., 2011), and trauma-related stimuli (Liberzon et al., 1999; Neumeister et al., 2017; Peres et al., 2011; Protopopescu et al., 2005; Shin et al., 2004), compared to trauma- and non-trauma-exposed healthy individuals. Some of these studies have also linked higher amygdala activation in response to negative emotional content to greater PTSD symptom severity (Brohawn et al., 2010; Neumeister et al., 2017; Protopopescu et al., 2005; Shin et al., 2004; St. Jacques et al., 2011). Together, these studies demonstrate the critical role of the amygdala in maladaptive fear responses central to PTSD-related psychopathology.

1.1. Aberrant task-related amygdala functional connectivity in PTSD

However, evidence suggests that complex mental health disorders such as PTSD may be better explained by understanding impaired interactions between brain regions rather than dysfunction of a single brain region (Fornito and Harrison, 2012). Functional connectivity, or examining correlated activity between brain regions, is one common analytic tool to explore co-activation patterns between brain regions. Studies have implicated aberrant functional connectivity (FC) between the amygdala and the dACC (Neumeister et al., 2017), hippocampus (Brohawn et al., 2010), and ventromedial prefrontal cortex (vmPFC) (Fonzo et al., 2010; Gilboa et al., 2004; Hayes et al., 2012; Simmons et al., 2011; St. Jacques et al., 2011; Stevens et al., 2013) in response to negative emotional information in PTSD. Connections between the amygdala and dACC have been found to facilitate fear expression, with a study demonstrating that individuals with PTSD show greater amydgala-dACC FC when exposed to trauma-related stimuli compared to non-trauma-exposed healthy controls (Neumeister et al., 2017). Additionally, another study showed that individuals with PTSD relative to trauma-exposed healthy individuals exhibit greater amygdala-hippocampus FC when processing and remembering non-trauma-related negative emotional pictures (Brohawn et al., 2010). Abnormal functioning of the amygdala-hippocampus neural circuit may contribute to trauma-related memory abnormalities and difficulties in contextually regulating fear responses. With respect to amygdala-vmPFC FC, some studies have found that individuals with PTSD show less\more negative amygdala-vmPFC FC in response to negative emotional stimuli compared to trauma-exposed or non-trauma-exposed healthy controls (Hayes et al., 2012; Stevens et al., 2013). However, others have found that individuals with PTSD relative to healthy controls show increased amygdala-vmPFC FC when processing trauma- or non-trauma-related negative emotional stimuli (Fonzo et al., 2010; Gilboa et al., 2004; Simmons et al., 2011; St. Jacques et al., 2011). The mixed findings across studies are likely impacted by differences in the type of emotional stimuli used (trauma- versus non-trauma-related, faces versus scenes, visual versus auditory), PTSD sample characteristics (civilian, veteran, type of trauma experienced), and whether trauma-exposed or non-trauma-exposed healthy controls served as the comparison group. Adaptive regulation of the amygdala by the vmPFC is vital for successfully regulating negative emotional responses (Motzkin et al., 2015). Thus, this circuit likely plays a critical role in poor emotion regulation seen in those with PTSD (Motzkin et al., 2015).

In addition to these core neural circuits, studies have implicated other regions including the somatosensory cortex (postcentral gyrus), visual cortex, primary motor cortex (precentral gyrus), and cerebellum in PTSD-related aberrant emotional processing (Nilsen et al., 2016; Simmons et al., 2011; St. Jacques et al., 2011). For example, some studies have found that individuals with PTSD show greater amygdala-somatosensory cortex and amygdala-visual cortex FC when encountering trauma-related stimuli or remembering negative emotional autobiographical memories (trauma- and non-trauma-related) compared to healthy trauma-exposed and non-trauma-exposed adults (Nilsen et al., 2016; St. Jacques et al., 2011). Additionally, less amygdala-cerebellum and amygdala-primary motor cortex FC in response to fearful faces have been found amongst those with PTSD compared to trauma-exposed healthy controls (Simmons et al., 2011). Supporting these findings, somatosensory processing abnormalities have been linked to PTSD (Badura-Brack et al., 2015; Geuze et al., 2007) and visual cortex dysfunction has been posited to play a role in hypervigilance, visual intrusions, and visual flashback symptoms (Clancy et al., 2017; Weston, 2014). An increasing number of studies have demonstrated cerebellar abnormalities amongst those with PTSD (Holmes et al., 2018; Rabellino et al., 2018; Thome et al., 2017). While the cerebellum has historically been recognized as playing a central role in motor control, it has also been found to play a role in cognitive and emotional functioning, and thus may play a role in emotional processing and cognitive impairments seen in PTSD (Buckner, 2013; Phillips et al., 2015). Collectively, these studies suggest that PTSD symptomology is related to aberrant amygdala functional connectivity with several brain regions when processing negative emotional material.

1.2. Amygdala resting state connectivity abnormalities in PTSD

Consistent with these task-based studies, resting state functional connectivity (RSFC) studies designed to examine pervasive neural communication abnormalities present even in the absence of threatening material, have also implicated abnormal amygdala RSFC. Studies have found that individuals with PTSD show less amygdala-vmPFC (Koch et al., 2016; Zhu et al., 2016) and amygdala-hippocampus RSFC (Sripada et al., 2012), but more positive/less anticorrelated, amygdala-dACC/dorsal mPFC RSFC (Birn et al., 2014; Brown et al., 2014; Koch et al., 2016; Sripada et al., 2012). However, other studies have found RSFC dysfunction between the amygdala with brain regions falling outside of traditional neural models of PTSD. These studies have shown that individuals with PTSD exhibit greater amygdala-primary motor cortex (Thome et al., 2017), and amygdala-insula RSFC (Rabinak et al., 2011; Sripada et al., 2012), the latter being involved in directing attention toward salient stimuli. Other studies have also found that those with PTSD relative to trauma-/non-trauma-exposed healthy controls, show less RSFC between the amygdala and cerebellum (Birn et al., 2014) as well as the posterior cingulate gyrus, a default mode network region implicated in self-referential processing and episodic memory retrieval (Bluhm et al., 2009). Together, both RSFC and task-based FC indicate that PTSD symptomology is associated with disrupted communication between the amygdala and brain regions critical for adaptive fear expression, emotional information processing, emotion regulation, memory, somatosensory processing, and motor functioning.

1.3. Neural predictors of risk for PTSD symptoms

While this prior work has provided important information about amygdala abnormalities linked to PTSD, all of these previous studies were cross-sectional and have focused on individuals who have already developed PTSD, which restricts the ability to identify neural markers that may predict risk for PTSD. Studies have begun to address this gap by examining whether brain activity/RSFC in the acute aftermath of a traumatic event can predict future PTSD symptom severity. Task-based studies have found that less response inhibition-related hippocampal activity (van Rooij et al., 2018) as well as greater amygdala (Stevens et al., 2016) and dACC (Wang et al., 2016), but less ventral ACC activity when viewing fearful stimuli (Stevens et al., 2016) during early trauma-

exposure was associated with increased future PTSD symptoms. Consistent with these findings, a study examining the brain activity of Boston-residing adolescents prior to the Boston marathon bombings, found that greater amygdala activation in response to negative emotional stimuli, but less hippocampus activation when trying to effortfully down-regulate emotional responses, was associated with greater PTSD symptomology after the Boston marathon bombings (McLaughlin et al., 2014). Regarding RSFC, one study found that greater early post-trauma amygdala-PCC RSFC predicted greater future PTSD symptoms (Lanius et al., 2010). Although another study found less amygdala-PCC RSFC predicted greater PTSD symptoms (Zhou et al., 2012). The purpose of this study was to expand on this sparse longitudinal work by assessing amygdala RSFC and FC during a script-guided trauma imagery fMRI task (e.g., Lanius et al., 2004) in the early aftermath of a traumatic event (two-week post-trauma) as potentially informative predictors of PTSD symptom severity six-month post-trauma. We expected that alterations in FC between the amygdala and core brain regions involved in the expression (dACC) and regulation (vmPFC, hippocampus) of fear responses would prospectively predict greater PTSD symptom severity. Specifically, during resting state, we expected to find that *less* amygdala-vmPFC and amygdala-hippocampus FC, but *greater* amygdala-dACC FC would predict greater post-trauma PTSD symptoms. However, for task-based analyses, we expected that *greater* amygdala-vmPFC, amygdala-hippocampus, and amygdala-dACC FC during recall of the trauma memory would be associated with greater six-month post-trauma PTSD symptom severity.

We also hypothesized that chronic PTSD symptoms may be predicted by amygdala-based circuits falling outside of the traditional fear network including connections between the amygdala and somatosensory cortex, visual cortex, motor cortex, cerebellum, insula, and posterior cingulate cortex. We expected that imaging predictors may significantly contribute to the prospective prediction of chronic PTSD symptomology, even after accounting for other potential demographic and clinical predictors of PTSD symptoms, such as female sex (Bonanno et al., 2007; Galea et al., 2008; Tolin and Foa, 2006), African American race (Roberts et al., 2011), younger age (Bonanno et al., 2007; Brewin et al., 2000), lack of education (Acierno et al., 1999; Brewin et al., 2000; although see Bonanno et al., 2007), prior trauma exposure (Brewin et al., 2000; Ozer et al., 2003), alcohol misuse (Acierno et al., 1999), depressive symptoms (Acierno et al., 1999; Bonanno et al., 2007; Freedman et al., 1999; Schnurr et al., 2004), and experiencing physical pain early post-trauma (Norman et al., 2008).

2. Methods and materials

2.1. Participants and procedures

All participants experienced a traumatic injury and received acute care from an urban emergency department (ED) of a Level 1 trauma center in Southeastern Wisconsin. Participants were included if they experienced a DSM-IV-TR, Criterion A traumatic event, were between the ages of 18–65, and were excluded if they had a head injury that resulted in loss of consciousness or had a Glasgow Coma Scale score < 13 (Teasdale and Jennett, 1974) on ED arrival. Participants were also excluded if they reported a lifetime history of psychosis or were taking antipsychotic medications. Prospective participants were identified via the ED discharge census and were screened over the phone to determine eligibility. Information about the trauma and trauma-related symptoms were gathered during the phone screen using the Acute Stress Disorder Structured Interview (Bryant et al., 1998) and the Life Events Checklist to assess lifetime trauma exposure (Gray et al., 2004). Eligible individuals were invited to sign the consent form, fill out self-report measures, and complete a resting state fMRI scan as well as a task-based scan involving listening to a script recounting details of their recent traumatic event two-weeks post-trauma (e.g., Lanius et al., 2004). Participants completed the same self-report measures again six-month post-trauma. The Institutional Review Board approved all study procedures. Two participants were excluded due to low self-reported alertness ratings throughout the scan, and seven participants did not complete the six-month follow-up. A final sample of 54 participants were included in either the resting state or the trauma recounting task fMRI analyses. A final sample of 49 participants had usable resting state fMRI data (five were excluded from analyses for having over 20% of their images dropped due to motion, five of the participants were not overlapping with the task fMRI analyses). Additionally, 49 participants were included in the task-analyses (two participants were dropped because they had 20% of their images dropped due to motion, three participants did not complete the task portion of the MRI, five of the participants did not overlap with the resting state fMRI analyses). Consistent with prior work (deRoon-Cassini et al., 2010; Zatzick et al., 2008), 25.93% of the sample likely suffered from clinically meaningful PTSD symptoms based on the Impact of Event Scale – Revised scores (IES-R; Weiss & Marmar, 1996; scores greater than 24 indicate clinically significant PTSD symptoms; See Table 1 for demographic and clinical information for the full sample $N = 54$).

Table 1
Sample characteristics.

Characteristic	Mean (SD) or %
Age, Years	33.22 (11.55)
Sex, Female %	65%
Race and Ethnicity %	
African American/Black	40.7%
Caucasian	48.1%
Hispanic	1.9%
Latino	1.9%
Native American	1.9%
Biracial	3.7%
No information provided	1.9%
Education %	
Graduated four-year college and beyond	20.4%
Some post-secondary education/college	42.6%
Completed high school	27.8%
Did not complete high school	7.4%
No education information provided	1.9%
Type of Trauma %	
Motor vehicle crash	75.9%
Physical Assault	18.5%
Other type of non-vehicular incident	5.6%
Trauma Load (# of past trauma types experienced)	7.66 (4.16)
Self-Reported Lifetime Psychopathology	
Depression and/or anxiety disorder	13.0%
Eating Disorder (Anorexia Nervosa)	1.9%
% at risk for alcohol use disorders (AUDIT-C)	40.7%
% current substance use (only marijuana endorsed)	5.6%
Medication	
% on Pain Medication	29.6%
% on psychotropic medication	18.5%
Two-week assessment symptoms	
Pain rating two-week post-trauma (0–10)	3.13 (2.34)
Depressive symptoms two-week post-trauma (BDI-II)	11.19 (8.08)
Anxiety symptoms two-week post-trauma (BAI)	12.16 (10.30)
PTSD symptoms two-week post-trauma (IES-R)	31.52 (18.49)
Six-month assessment symptoms	
PTSD symptoms six-month post-trauma (IES-R)	19.01 (20.79)
% Clinically Significant PTSD symptoms (IES-R > 24)	25.93%
Probable DSM-IV PTSD Diagnosis (IES-R > 33)	16.67%

Note: AUDIT- C = Alcohol Use Disorders Identification Test- Consumption (a score ≥ 3 for females and a score of ≥4 for males is considered to be an indicator of problematic drinking) BDI-II = Beck Depression Inventory; BAI = Beck Anxiety Inventory; IES-R = Impact of Event Scale – Revised Psychotropic medications included use of SSRIs (9.3%), SNRI's (3.7%), Tricyclic antidepressants (1.9%), and benzodiazepines (9.3%).

2.2. Self-report instruments

Participants completed the IES-R (Weiss & Marmar, 1996), the Beck

Depression Inventory-II (BDI-II; Beck et al., 1996), the Beck Anxiety Inventory (BAI; Beck and Steer, 1993), the Visual Analogue Scale for Pain (VAS Pain, McCormack, et al., 1988), and the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C, Busch et al., 1998; Bradley et al., 2003) at two-weeks post-trauma and six-months post-trauma. The IES-R, demonstrated to have high internal consistency and test-retest reliability (Beck et al., 2008), is a 22-item scale that assesses posttraumatic stress symptoms. Items are rated on a 0 (not at all) to 4 (extremely) scale with respect to symptom distress, with total scores ranging from 0 to 88. The BDI-II consists of 21-items assessing depressive symptoms, with each item rated on a 0–3 scale. The Beck Anxiety Inventory is a 21-item self-report inventory of common anxiety symptoms, with each item rated on a 0 (not at all) to 3 (severe) scale. The VAS pain scale is a measure of unidimensional pain (Downie et al., 1978; Ferraz et al., 1990); participants rate their pain level on a continuous 0 (no pain) −10 (worst pain) scale. The AUDIT-C assesses the presence and severity of an alcohol problem and consists of three questions on a five-point Likert scale, with scores ranging from 0 to 12. A score of ≥3 for females and ≥4 for males is thought to indicate a potential alcohol use problem (Busch et al., 1998; Bradley et al., 2003).

2.3. MRI procedures

Participants completed a T1-weighted structural scan, a resting state fMRI scan, and a script driven imagery fMRI scan two-weeks post-trauma. During the resting state scan, participants viewed a black screen and were instructed to keep their eyes open. Following the resting state scan, participants completed a well-established script driven imagery task (Lanius et al., 2001, 2002; 2004, 2005). For each participant, brief auditory scripts about their trauma were generated based on the trauma details that were collected during the screening. Additionally, a neutral script based on a recent event from the participant's life was also created. In the scanner, each trial consisted of: a.) a 60 s baseline period in which a fixation cross was presented, b.) a 30 s auditory presentation of the script, c.) a 30 s guided imagery/recall period during which participants were asked to focus on the olfactory, auditory, somatosensory, and visual sensations associated with the event and d.) a 60 s relaxation period in which participants were asked to lie still and let go of the event. Consistent with prior work (e.g., Hopper et al., 2007; Lanius et al., 2004), participants first completed three trials of the neutral imagery script followed by three trials of the trauma imagery script.

2.4. Imaging acquisition

Twenty-six participants completed their scanning session on a 3T Tesla long bore GE Signa Excite MRI system and twenty-eight participants completed their scan on a 3 T short bore GE Signa Excite MRI system, both located at the Medical College of Wisconsin. Functional images were acquired using a T2* weighted gradient-echo, echoplanar pulse sequence. On the long bore scanner, a 6-min resting state fMRI scan was conducted with 38 interleaved slices collected in a sagittal orientation with the following parameters: repetition time (TR)/echo time (TE) = 2000/25 ms; field of view (FOV) = 240 mm; matrix = 64 × 64; flip angle = 77°; slice thickness = 3.7 mm; 21 participants scanned on the long bore were included in the resting state fMRI analyses. On the short bore scanner, a 5-min resting state fMRI scan was conducted with 41 interleaved slices collected with the following parameters: TR/TE = 2000/25 ms; FOV = 240 mm; matrix = 64 × 64; flip angle = 77°; slice thickness = 3.5 mm; 28 participants scanned on the short bore were included in the resting state fMRI analyses. A high-resolution T1-weighted anatomical image was also acquired with the following parameters, identical for both scanners: TR/TE = 8.2/3.2 ms; FOV = 240 mm; matrix = 256 × 224; flip angle = 12°; voxel size = 0.9375 × 0.9375 × 1 mm. The same fMRI parameters for the script driven imagery task were used on both scanners: (TR)/echo time (TE) = 2000/25 ms; FOV = 240 mm, matrix = 64 × 64; flip angle = 77°; slice thickness = 3.7 mm (long bore), 3.5 mm (short bore); number of slices = 38 (long bore), 41 (short bore). Twenty-five participants completing their scan on the long bore scanner and twenty-four participants completing their scan on the short bore scanner were included in the script driven imagery fMRI analyses.

2.5. fMRI pre-processing

The same preprocessing steps were conducted for both resting state and script driven imagery data. The first 6 s of each participant's resting state and script driven imagery functional data were dropped to allow for magnetic field stabilization. All fMRI data were preprocessed in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/), which included slice-time correction, realignment, normalization to Montreal Neurological Institute (MNI) space, and resampling to 2 × 2 × 2 mm voxels and smoothing with a 6-mm kernel. The artifact detection tool box (https://www.nitrc.org/projects/artifact_detect/) was used to identify motion-related outlier data points. Outlier data points for resting state fMRI were defined as volumes that exceeded a global mean intensity of three standard deviations away from the mean intensity across functional runs, or a composite threshold of 0.5 mm framewise displacement. Motion-related outlier data points for the script driven imagery task fMRI data were defined as volumes that exceeded a global mean intensity of three standard deviations away from the mean intensity across functional runs, or a composite threshold of 2 mm framewise displacement. Participants who had over 20% of their data points marked as outliers, were dropped from analyses (five participants were dropped from RSFC analyses and two participants were dropped from task-based FC analyses).

2.5.1. fMRI first-level analysis

Additional pre-processing steps and seed (with the right and left amygdala as the seeds) to whole-brain voxel FC analyses during rest and task were conducted using the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). Physiological noise from white matter and cerebrospinal fluid was estimated and regressed out for each participant using the CompCor method (Behzadi et al., 2007). In a first-level hemodynamic response function (HRF)- weighted general linear model (GLM), detrending, modeling of outlier images along with the three translation and three rotation parameters, plus one composite motion parameter indexing the maximum scan-to-scan movement and the ComCor corrections were conducted simultaneously. Then a 0.008-0.09 Hz temporal band-pass filter was applied to the time series.

For task-based data, each condition (script, guided/imagery recall, post-recall relaxation) within each block (trauma, neutral) was convolved with the canonical HRF to define corresponding condition-specific weights. Both weighted GLM and generalized psychophysiological interaction (gPPI) analyses are common approaches for examining FC in task-based block fMRI designs, (e.g., Ismaylova et al., 2018; Kaiser et al., 2019; Poletti et al., 2018). While both weighted-GLM and gPPI can provide “relative” measures of FC, comparing one condition to another condition or to an implicit baseline, a weighted-GLM can also provide “absolute” measures of FC occurring during a single task condition, via a nonparametric estimation of weighted correlation measures within each condition. Both “absolute” and “relative” FC measures derived from a weighted GLM are thought to provide complementary and useful information, and thus both have been reported in the literature (e.g., Poletti et al., 2018). Additionally, a recent study demonstrated that neural difference scores (i.e., contrasting brain activation in one task condition compared to the other task condition) may show poorer reliability compared to examining conditions separately (Infantolino et al., 2018), further supporting the value of examining “absolute” FC in addition to “relative” measures to examine associations with individual differences in PTSD symptomology.

To generate amygdala-whole-brain correlation maps during rest and

task conditions, the time series was extracted separately from right and left amygdala seeds, which were taken from the Harvard-Oxford probabilistic atlas in the CONN toolbox (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006), and correlated with every other voxel in the brain. The whole-brain correlation maps (*r*) were normalized using a Fischer's *z* transformation and were used to calculate all group-level statistics.

2.6. Group-level statistics

For RSFC analyses, we conducted multiple linear regression analyses to examine whether two-week left and right amygdala RSFC separately predicted total PTSD symptoms at 6-months when controlling for MRI scanner type. This same set of multiple linear regression analyses were applied to FC during neutral script imagery and trauma script imagery separately to examine absolute connectivity measures for each task condition. Consistent with prior studies, the script driven imagery fMRI analyses focused on the 30-s guided imagery recall period (e.g., Lanius et al., 2001, 2002; 2004, 2005). We also examined "relative" measures of connectivity directly comparing differences between the trauma and neutral conditions in their association with six-month PTSD symptoms to assess for specificity of the findings to trauma recall. Six-month IES-R PTSD symptom scores were positively skewed (greater than + 1.5) and were normalized using a square root transformation. All results were considered significant if they passed a voxel threshold $p < 0.001$ cluster corrected to a FWE error rate of 0.025 (to correct for separate tests being conducted on left and right amygdala seeds).

After identifying amygdala-whole brain RSFC and script driven imagery FC associated with PTSD symptoms six-month post-trauma, we conducted follow-up sensitivity analyses using SPSS Version 24 to test the robustness of amygdala FC associations with six-month post-trauma PTSD symptoms. Two separate multiple linear regressions were conducted to examine whether amygdala RSFC and script driven imagery FC survived as significant predictors of six-month post-trauma PTSD symptoms after accounting for other potential predictors of PTSD described in the literature. These predictors included: 1.) scanner type (dummy coded covariate) 2.) demographics (sex, age, education (dichotomous; grouping those who completed any post-secondary education versus those who only completed high school or below)), ethnicity (White, African American, Other); 3.) trauma-related variables (type of current trauma (motor vehicle crash, other type of non-vehicular incident, physical assault), trauma load (number of past traumas experienced); 4.) two-week post-trauma symptom severity (PTSD symptoms, depressive symptoms, general anxiety symptoms, pain severity, problematic drinking) and 5.) medication status (pain medication (coded as 0 or 1 for not taking versus taking medication), psychotropic medication (coded as 0 or 1 for not taking versus taking medication)).

3. Results

3.1. RSFC and imagery task FC predictors of six-month PTSD symptoms

We found that greater PTSD symptom severity was predicted by more negative left amygdala – left postcentral gyrus (extending into precentral gyrus) RSFC (−46, −30, +52; 518 voxels; FWE $p = 0.000003$) as well as more negative right amygdala – right cerebellum RSFC (+14, −78, −52, 176 voxels, FWE $p = 0.01$; +12, −50, −26, 150 voxels, FWE $p = 0.022$) when controlling for MRI scanner type (See Fig. 1). With regard to "absolute measures" of amygdala FC during the trauma script driven imagery task, we found that more negative left amygdala – left midcingulate FC (-8 -14, +38, 299 voxels, 0.000095) and more negative right amygdala – right postcentral/precentral gyrus (+46, −16, +42, 169 voxels, FWE $p = 0.004$) predicted greater six-month PTSD symptom severity when controlling for MRI scanner type (See Fig. 2). We did not find any significant "absolute measures" of amygdala FC predictors of six-month post-trauma PTSD symptoms during neutral script imagery trials.

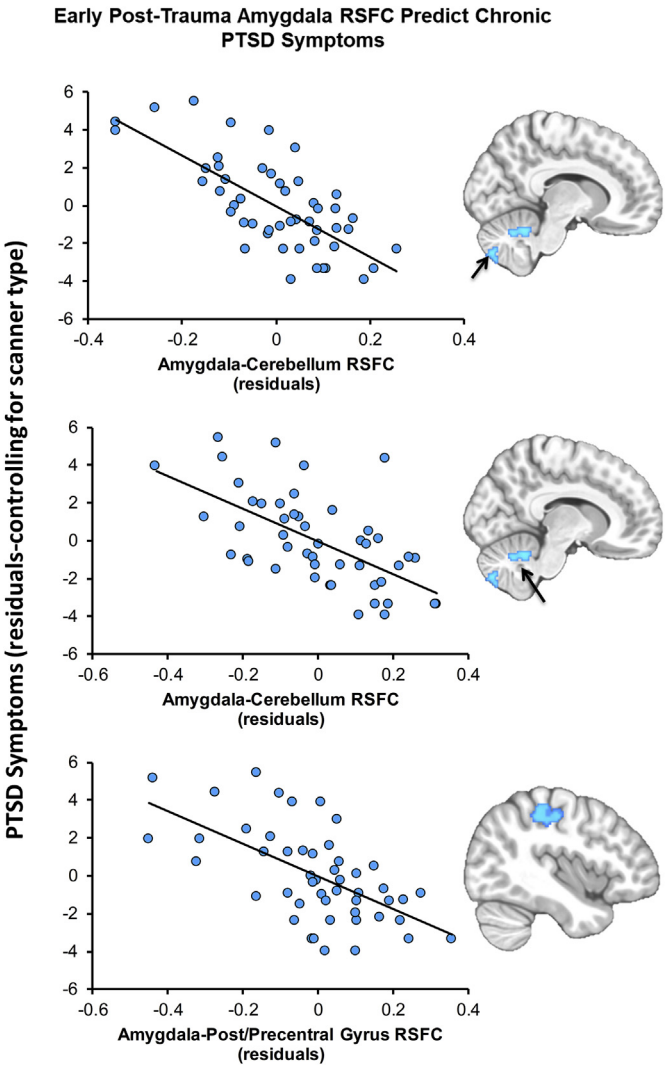

Fig. 1. Early post-trauma amygdala resting state functional connectivity (RSFC) predicted greater six-month post-trauma PTSD symptom severity.

We also examined "relative measures" of functional connectivity to better determine whether associations between right amygdala – right postcentral/precentral gyrus FC and left amygdala – left midcingulate FC during trauma recall with six-month post-trauma PTSD symptoms were specific to trauma processing. To do this, we extracted the same right amygdala – right postcentral/precentral gyrus and left amygdala-left midcingulate functional connectivity measures (Fischer's r to z normalized correlation values) during neutral recall. We then conducted two repeated measure ANOVAs to assess for possible Condition (Trauma, Neutral) x six-month PTSD symptom score interactions. With regard to right amygdala – right postcentral/precentral gyrus FC, we found a significant Condition x six-month PTSD symptom score interaction, F (1,46) = 13.170, p = .001. Follow-up linear regressions showed that lower right amygdala – right postcentral/precentral gyrus FC during trauma recall significantly predicted six-month trauma symptoms (β = −0.639, t = −5.693, p < .001). However, right amygdala – right postcentral/precentral gyrus FC during neutral recall did not significantly predict six-month PTSD symptoms (β = -.224, t = −1.58, p = 0.122). With respect to left amygdala – left midcingulate FC, we failed to find a significant Condition x six-month PTSD symptom score interaction, F (1,46) = 2.238, p = 0.141. Indeed, follow-up regressions showed that more negative left amygdala –

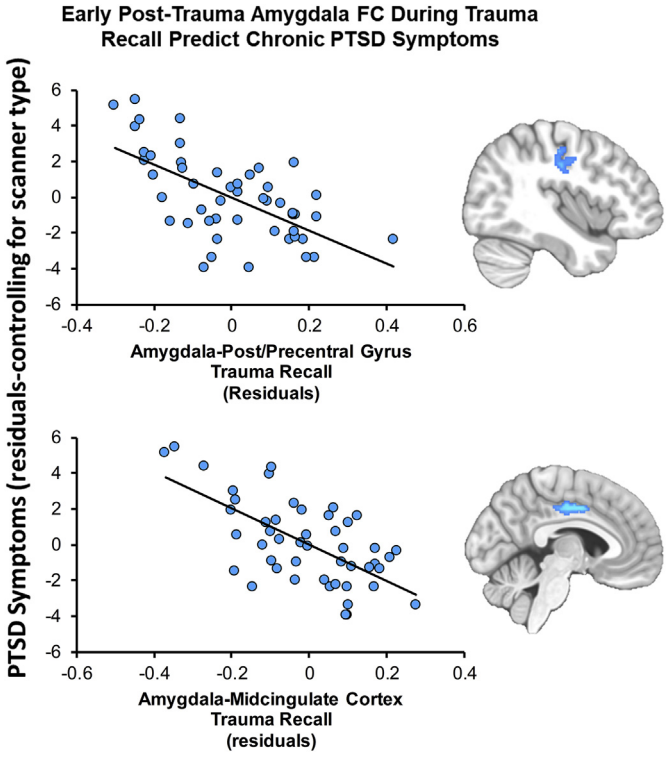

Fig. 2. Early post-trauma amygdala functional connectivity when recounting the traumatic event (script driven imagery task) predicted greater six-month post-trauma PTSD symptom severity.

midcingulate FC during trauma recall ($\beta = -.650$, $t = -5.871$, $p < .001$) and during neutral recall ($\beta = -.420$, $t = -3.176$, $p = .003$) both predicted six month PTSD symptoms, although the relationship between six-month PTSD symptoms and amygdala – midcingulate FC during neutral recall was weaker than during trauma recall. A similar pattern emerged at a whole-brain level although with a less conservative multiple comparison threshold (voxel-threshold of $p < 0.05$, cluster corrected FWE $p < 0.05$), with more negative right amygdala – right postcentral/precentral gyrus FC during trauma recall relative to neutral recall predicting greater six-month PTSD symptoms. This pattern did not emerge for left amygdala – left midcingulate at the whole-brain level. This suggests that associations between PTSD symptoms and amygdala-postcentral/precentral gyrus are likely specific to trauma processing, but associations with amygdala-midcingulate FC may reflect a more general memory recall process.

3.2. Follow-up sensitivity analyses

In the first model incorporating RSFC variables, more negative right amygdala-right cerebellum (+14, −78, −52; $\beta = -0.395$, $B = -7.293$, $t = -3.428$, $p = .002$) survived after accounting for the other demographic, clinical, and trauma-related predictors. However, less amygdala-left postcentral gyrus RSFC as a predictor of chronic PTSD symptoms dropped to a trend level ($\beta = -0.251$, $B = -3.342$, $t = -1.966$, $p = 0.060$) and amygdala RSFC with the other cerebellar cluster did not survive after accounting for the other predictors (+12, −50, −26; $\beta = -0.097$, $B = -1.351$, $t = -0.836$, $p = 0.411$; See Table 2). With respect to the second model including "absolute" measures of amygdala FC during trauma script driven imagery, more negative right amygdala - right postcentral/precentral gyrus FC when recalling the traumatic event in the scanner predicted greater 6-month PTSD symptomology ($\beta = 0.337$, $B = -4.720$, $t = -2.207$, $p = .036$). Additionally, there was a non-significant trend for lower left amygdala-left midcingulate connectivity predicting greater six-month PTSD symptoms ($\beta = -0.322$, $B = -4.487$, $t = -1.909$, $p = 0.067$) when accounting for the other predictors (See Table 3). To make sure that the three participants endorsing regular marijuana use were not driving our results, we re-ran the multiple linear regression sensitivity analyses without these participants. The results remained the same after the

Table 2
Sensitivity analyses to test the robustness of RSFC-six-month post-trauma PTSD symptom associations when accounting for other relevant demographic, clinical, and trauma-related predictors.

Predictor	*B*	*β*	*t*	*p*
MR Scanner Type	−0.660	−0.139	−1.319	0.198
Age	0.001	0.005	0.052	0.959
Sex (male/female)	−1.458	−0.284	−2.819	0.009[a]
Education (post-secondary/no post-secondary)	−0.020	−0.004	−0.033	0.974
African American Race (versus Caucasian)	0.618	0.129	1.108	0.278
Other Minority Race (versus Caucasian)	−1.123	−0.147	−1.299	0.205
Physical Assault (versus motor vehicle crash)	1.342	0.225	1.839	0.077
Other non-vehicular incident (versus motor vehicle crash)	−0.612	−0.064	−0.476	0.638
Trauma Load	−0.044	−0.077	−0.655	0.518
Psychotropic Medication	0.053	0.008	0.070	0.944
Pain Medication	0.203	0.040	0.403	0.690
Two-Week PTSD Symptoms (IES-R)	0.013	0.099	0.598	0.555
Two-Week Depressive Symptoms (BDI-II)	0.077	0.256	1.885	0.070
Two-Week Anxiety Symptoms (BAI)	0.034	0.145	1.050	0.303
Two-Week Pain Rating	0.042	0.040	0.382	0.706
Alcohol Use (AUDIT-C)	0.026	0.023	0.223	0.825
Right Amygdala – Right Cerebellum RSFC (+14, −78, −52)	−7.293	−0.395	−3.428	0.002[a]
Right Amygdala – Right Cerebellum RSFC (+12,-50, −26)	−1.351	−0.097	−0.836	0.411
Left Amygdala – Left Postcentral/ Precentral Gyrus RSFC	−3.342	−0.251	−1.966	0.060

[a] $p < .05$ More negative right amygdala -right cerebellum resting state functional connectivity (RSFC) survived as a predictor of six-month post-trauma PTSD symptom severity.

Table 3
Sensitivity analyses to test robustness of trauma imagery task FC - six month post-trauma PTSD symptom assocations when accounting for other relevant demographic, clinical, and trauma-related predictors.

Predictor	*B*	*β*	*t*	*p*
MR Scanner Type	−0.173	−0.038	−0.256	0.800
Age	0.012	0.059	0.510	0.614
Sex (male/female)	−1.104	−0.221	−1.657	0.109
Education (post-secondary/no post-secondary)	−0.280	−0.056	−0.387	0.702
African American Race (versus Caucasian)	1.087	0.231	1.592	0.123
Other Minority Race	0.008	0.001	0.008	0.994
Physical Assault (versus motor vehicle crash)	0.929	0.153	0.998	0.327
Other non-vehicular incident (versus motor vehicle crash)	−2.031	−0.179	−0.995	0.328
Trauma Load	−0.097	−0.170	−1.138	0.265
Psychotropic Medication	0.663	0.109	0.686	0.498
Pain Medication	0.697	0.136	1.026	0.314
Two-Week PTSD Symptoms (IES-R)	0.014	0.112	0.599	0.554
Two-Week Depressive Symptoms (BDI-II)	−0.044	−0.143	−0.853	0.401
Two-Week Anxiety Symptoms (BAI)	0.070	0.304	1.615	0.118
Two-Week Pain Rating	0.062	0.062	0.410	0.685
Alcohol Use (AUDIT-C)	0.155	0.130	1.001	0.326
Right Amygdala – Right Precentral/ Postcentral Gyrus FC	−4.720	−0.337	−2.207	0.036*
Left Amygdala – Left Midcingulate FC	−4.487	−0.322	−1.909	0.067

*$p < .05$ More negative right amygdala – right precentral/postcentral gyrus functional connectivity (FC) survived as a significant predictor of six-month post-trauma PTSD symptom severity.

removal of these participants.

4. Discussion

The primary goal of this study was to examine whether amygdala whole-brain FC at rest and while recalling the traumatic event two-weeks after trauma exposure could predict six-month post-trauma PTSD symptom severity. Overall, our findings indicate that amygdala FC measured in the acute period following trauma prospectively predicts risk for PTSD symptoms. Surprisingly, we did not find that aberrant acute trauma-related FC of the amygdala with dACC, vmPFC, and hippocampus predicted greater PTSD symptoms. While there is support for abnormal functional interactions between these brain regions in PTSD (e.g., Birn et al., 2014; Brohawn et al., 2010; Neumeister et al., 2017; Sripada et al., 2012; Stevens et al., 2013; Zhu et al., 2016), several RSFC and task-based fMRI studies involving viewing negative emotional material have failed to find PTSD-related impairment of this circuitry (e.g., Fani et al., 2016; Nilsen et al., 2016; Rabinak et al., 2011). Furthermore, based on existing evidence, Admon et al., 2013 proposed that some of the disrupted communication occurring between the amygdala, hippocampus, mPFC, and ACC may occur only after PTSD is fully developed. Given that we examined FC in the early phases of trauma-exposure prior to full PTSD development, it is possible that disruptions in this neural circuitry were not yet apparent.

However, with respect to RSFC, we did find that less amygdala-cerebellum and amygdala-postcentral/precentral gyrus in the early aftermath of trauma predicted greater six-month PTSD symptomology when controlling for MRI scanner type. Less amygdala-cerebellum RSFC survived as a predictor in the follow-up sensitivity analyses when accounting for several other relevant demographic and clinical predictors. While the cerebellum has been traditionally implicated in motor control, more recent studies have provided evidence of a broader role for the cerebellum, including an involvement in emotional and cognitive functioning (Buckner, 2013; Phillips et al., 2015). Human studies have found that lesions of the cerebellum can produce anxiety, irritability, and distractibility; symptoms relevant to PTSD (Buckner, 2013). Additionally, an increasing number of studies have documented cerebellum abnormalities amongst those with PTSD (Holmes et al., 2018; Rabellino et al., 2018; Thome et al., 2017), including lower amygdala-cerebellum FC (Simmons et al., 2011). Human neuroimaging studies have documented functional connections between the amygdala and cerebellum (Gabard-Durnam et al., 2014; Sang et al., 2012), with preclinical studies providing evidence that amygdala-cerebellum connections may be critical for fear learning and the consolidation as well as maintenance of fear memories (Sacchetti et al., 2007; Zhu et al., 2011). Although the precise link between amygdala-cerebellum connections and PTSD pathophysiology remains unclear, this preclinical evidence suggests that amygdala-cerebellar FC alterations may contribute to abnormal processing of trauma memories. With respect to amygdala-precentral/postcentral gyrus connectivity, a diffusion tensor imaging study documented direct connections between the amygdala and precentral gyrus as well as postcentral gyrus (Grezes et al., 2014), with a recent RSFC study providing evidence of a distinct amygdala-somatosensory/premotor cortex neural network (Toschi et al., 2017). Researchers have theorized that functional connections between the amygdala and somatosensory/premotor cortex may underlie emotional modulation of subjective sensory experiences (Damasio, 1994, 2001). While less studied in relationship to PTSD symptoms, there is some initial evidence of disrupted amygdala-precentral/postcentral RSFC amongst those with PTSD (Thome et al., 2017), which may reflect maladaptive somatosensory processing.

Amygdala FC during a script-guided trauma imagery fMRI task early post-trauma also predicted greater PTSD symptom severity six-month post-trauma. Specifically, less amygdala-precentral/postcentral gyrus and less amygdala-midcingulate cortex (MCC) FC during trauma recall in the acute aftermath of trauma exposure predicted greater six-month PTSD symptom severity. The follow-up sensitivity analyses demonstrated that less amygdala precentral/postcentral gyrus FC when recalling the traumatic event survived as a significant predictor of chronic PTSD symptoms when accounting for the other covariates. Functional neuroimaging studies in healthy individuals have demonstrated that amygdala, somatosensory cortex, and premotor cortex regions co-activate when processing emotional stimuli (Conty et al., 2012; de Gelder et al., 2004; Grosbras and Paus, 2006; Pichon et al., 2008; Pichon et al., 2009; Van den Stock et al., 2011). Additionally, transcranial magnetic stimulation studies provide evidence that emotionally evocative stimuli known to activate the amygdala, also signal the motor-related/somatosensory brain regions to promote adaptive responding to the emotional material (Baumgartner et al., 2007; Coelho et al., 2010; Coombes et al., 2009; Hajcak et al., 2007; Oliveri et al., 2003; van Loon et al., 2010). Somatosensory and primary motor cortex disturbances have been reported in PTSD, including alterations in amygdala-precentral/postcentral gyrus FC when viewing negative emotional or trauma-related stimuli (Nilsen et al., 2016; Simmons et al., 2011). Granted the direction of the findings is mixed in prior PTSD studies, more negative early post-trauma amygdala-postcentral/precentral gyrus connectivity may reflect an early risk marker for maladaptive responding to emotional stimuli, such as avoidance, a core facet of PTSD.

Although the amygdala, dACC, vmPFC, and hippocampus are more frequently discussed in conceptualizations of PTSD, a meta-analysis found that the midcingulate cortex is also a part of a core network of brain regions involved in PTSD (Boccia et al., 2016). The posterior midcingulate, the portion of the cingulate cortex that was found to show less connectivity with the amygdala with greater six-month post-trauma symptom severity, has been shown to be involved in preparing the body to respond to potentially harmful stimuli (Vogt, 2016) and in the recall of painful experiences (Fairhurst et al., 2012). Thus, aberrant amygdala-posterior midcingulate FC may play a part in maladaptive recall of and responding to trauma related stimuli or cues in those who are experiencing chronic PTSD symptoms. However, “relative” measures of connectivity directly comparing the recall of trauma imagery versus neutral imagery found that aberrant amygdala-midcingulate FC during neutral recall was also predictive of greater six-month PTSD symptoms. Thus, PTSD-related amygdala-midcingulate FC abnormalities may reflect a more general maladaptive memory recall process. Consistent with this, a study found that participants with PTSD recruited less cingulate cortex activation during a non-emotional declarative memory recall task (Chen et al., 2009). Together these results suggest that alterations in FC between the amygdala with regions involved in somatosensory processing, motor functioning, emotion processing, and cognitive functioning may be important neural vulnerability markers of risk for experiencing chronic PTSD symptoms. These early post-trauma neural markers may potentially facilitate PTSD risk by supporting dysfunctional fear responses.

5. Conclusion

The study has many strengths, including the prospective design, and the relatively large sample size compared to previously published longitudinal neuroimaging studies in PTSD. However, there are several limitations. A portion of the sample was taking pain and antidepressant/antianxiety medications. While we controlled for medication in our analyses and medication did not appear to be significantly driving relationships between FC and six-month post-trauma PTSD symptoms, we cannot entirely rule out the potential influence of those medications on brain functioning. Additionally, over 75% of our sample endorsed a motor vehicle crash as being their Criterion A traumatic event, and only 26% of our sample reported experiencing clinically meaningful PTSD symptoms post-trauma, which may limit the generalizability of our findings. That said, the percentage of individuals experiencing clinically relevant PTSD symptoms in our study is consistent with other trauma outcome investigations (deRoon-Cassini et al.,

2010; Zatzick et al., 2008). We also did not assess other possible important predictors of PTSD, including experiencing childhood trauma, and we relied on the use of self-report measures of trauma symptoms and lifetime psychiatric diagnoses, rather than clinician-delivered diagnostic interviews. Due to the phasing out of a scanner for research, our study was conducted using two GE 3T scanners. Consistent with other studies pooling data from different scanners (e.g., Kaiser et al., 2016), we assessed for and controlled for potential scanner type differences in all of our FC analyses. We failed to find significant scanner type differences in FC, suggesting that site differences are likely not significantly driving relationships between FC and PTSD symptomology. Congruent with our findings, other multisite studies pooling data from different scanners have reported minimal effects of scanner differences in both RSFC (e.g., Noble et al., 2018) and emotional processing tasks (Gee et al., 2015). While our analyses suggest that scanner type differences are likely not influencing our findings, we cannot entirely rule out all potential scanner type effects on the data. Despite these limitations, our study provides novel evidence of amygdala FC in the acute aftermath of a traumatic event prospectively predicting more chronic PTSD symptoms six-months post-trauma. These results highlight the critical role of disrupted neural communication involving the amygdala in the acute aftermath of trauma and most notably prospective prediction of risk for chronic posttraumatic distress. These findings provide a foundation for future work establishing early biomarkers of risk for PTSD, which may lead to earlier intervention and more specific mechanism-based preventative interventions.

Author contributions

Emily L. Belleau: Formal analysis; Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. Lauren E. Ehret: Data curation, Writing - review & editing, Project administration. Jessica L. Hanson: Data curation, Writing - review & editing, Project administration. Karen J. Brasel: Writing - review & editing, Christine L. Larson: Conceptualization, Writing - review & editing, Supervision, Funding acquisition. Terri A. deRoon-Cassini: Conceptualization, Writing - review & editing, Supervision, Funding acquisition.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

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