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Thalamic volume and fear extinction interact to predict acute posttraumatic stress severity

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ABSTRACT

Posttraumatic stress disorder (PTSD) is associated with lower gray matter volume (GMV) in brain regions critical for extinction of learned threat. However, relationships among volume, extinction learning, and PTSD symptom development remain unclear. We investigated subcortical brain volumes in regions supporting extinction learning and fear-potentiated startle (FPS) to understand brain-behavior interactions that may impact PTSD symptom development in recently traumatized individuals. Participants ($N = 99$) completed magnetic resonance imaging and threat conditioning two weeks following trauma exposure as part of a multisite observational study to understand the neuropsychiatric effects of trauma (AURORA Study). Participants completed self-assessments of PTSD (PTSD Checklist for DSM-5; PCL-5), dissociation, and depression symptoms two- and eight-weeks post-trauma. We completed multiple regressions to investigate relationships between FPS during late extinction, GMV, and PTSD symptom development. The interaction between thalamic GMV and FPS during late extinction at two weeks post-trauma predicted PCL-5 scores eight weeks (t (75) = 2.49, $\beta = 0.28$, $p = 0.015$) post-trauma. Higher FPS predicted higher PCL-5 scores in the setting of increased thalamic GMV. Meanwhile, lower FPS also predicted higher PCL-5 scores in the setting of decreased thalamic GMV. Thalamic GMV and FPS interactions also predicted posttraumatic dissociative and depressive symptoms. Amygdala and hippocampus GMV by FPS interactions were not associated with posttraumatic symptom development. Taken together, thalamic GMV and FPS during late extinction interact to contribute to adverse posttraumatic neuropsychiatric outcomes. Multimodal assessments soon after trauma have the potential to distinguish key phenotypes vulnerable to posttraumatic neuropsychiatric outcomes.

1. Introduction

Posttraumatic stress disorder (PTSD) affects approximately 6.8% of the United States population (Kessler et al., 2005) with consequences for individuals and society (Kessler, 2000). Early interventions improve and mitigate the development of PTSD (Kearns et al., 2012; Rothbaum et al., 2012). However, the high rate of trauma exposures in the general population and variability in individual susceptibility to PTSD make it costly and inefficient to provide intensive early interventions to every traumatized individual (Kilpatrick et al., 2013). Early identification of individuals susceptible to PTSD following trauma exposure is thus crucial for the development of efficient early intervention strategies (Kearns et al., 2012; McLean et al., 2019).

Chronic PTSD is associated with disruptions in threat learning processes that are commonly studied with Pavlovian fear conditioning. In healthy adaptive learning, individuals both acquire new threat memories when danger is present and extinguish the memory once danger has passed. Individuals with PTSD, however, show an enhanced ability to acquire, but a reduced ability to extinguish, fear conditioned memories (Jovanovic et al., 2012; Norrholm et al., 2011).

Fear-potentiated startle (FPS) is a robust psychophysiological measure of threat learning and autonomic reactivity, indexed by an increased startle response in the presence of a danger signal. PTSD is associated with exaggerated FPS to a conditioned stimulus (CS) during acquisition that persists during extinction (Grillon and Morgan, 1999; Jovanovic et al., 2012; Norrholm and Jovanovic, 2018). However, increasing attention is being paid to heterogeneity within PTSD, with differences in extinction patterns potentially aiding in defining PTSD subgroups (Galatzer-Levy et al., 2013; Seligowski et al., 2019).

Subcortical/deep cortical neural circuitry, including the amygdala, hippocampus, and thalamus, play an important role in the acquisition, expression, and extinction of conditioned fear (Barad et al., 2006; Fanselow and Ledoux, 1999; Maren, 2001; Phelps et al., 2004). The basolateral nucleus of the amygdala receives sensory input from the thalamus and cortex (Senn et al., 2014) and connects to the central nucleus of the amygdala, which mediates autonomic responses to threat (Gafford and Ressler, 2016; Krabbe et al., 2018). Amygdala-dependent extinction learning is then modulated by the hippocampus to facilitate the formation and contextualization of extinction memories (Ji and Maren, 2007; Knight et al., 2004; LaBar and Phelps, 2005; Liu et al., 2012; Rudy et al., 2004; Senn et al., 2014). Thalamic connections to the amygdala and hippocampus also critically relay extinction-related sensory information necessary to form an inhibitory memory (Fanselow and Ledoux, 1999; Galatzer-Levy et al., 2013; Lee et al., 2019; Lee et al., 2012; Ramanathan and Maren, 2019; Troyner et al., 2018). Together, the amygdala, hippocampus, and thalamus constitute key subcortical circuitry for extinction learning.

This set of regions show structural morphometric alterations in chronic PTSD. Decreased amygdala gray matter volume (GMV) have been seen in those with prior trauma histories and PTSD (Ganzel et al., 2008; Logue et al., 2018; O'Doherty et al., 2015). Meta-analyses have demonstrated diminished hippocampal GMV in PTSD (Bromis et al., 2018; Kitayama et al., 2005; Kühn and Gallinat, 2013; Logue et al., 2018; Woon et al., 2010). Although decreased thalamic GMV was not observed in meta-analyses of PTSD that combined military and civilian trauma (Bromis et al., 2018; Kitayama et al., 2005; Logue et al., 2018), smaller thalamic GMVs have been observed in civilians with PTSD (O'Doherty et al., 2017), dissociation (Daniels et al., 2015), and intrusion symptoms (Shucard et al., 2012). In sum, lower volumes of the amygdala, hippocampus, and thalamus have been consistently linked with trauma exposure and PTSD symptoms.

No prior work has assessed for a potential relationship between GMV and FPS during extinction in the acute aftermath of trauma or if associations between GMV and FPS relate to future posttraumatic symptom expression. We thus hypothesized that examining both behaviors and brain structures in the early aftermath of trauma exposure and evaluating their association with later PTSD symptom development would

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help identify posttraumatic stress vulnerability phenotypes. By focusing on neural integrity in regions critically implicated in extinction, we may gain mechanistic insight regarding neurophysiological mechanisms acutely that are relevant to the maintenance of later chronic symptoms.

In the present study, we investigated putative relationships among subcortical GMV, physiological reactivity (indexed via FPS), and acute PTSD symptoms following trauma exposure. Late extinction, the time when inhibitory learning should be strongest, has been utilized as a marker of treatment success for PTSD (Rousseau et al., 2019). We therefore hypothesized that FPS during late extinction would relate to lower amygdala, hippocampus, and thalamus GMV. Further, we postulated that the interaction of thalamus, amygdala, and hippocampus GMV and FPS during late extinction would be prospectively associated with PTSD symptom severity eight-weeks following trauma exposure. The interaction of GMV-FPS on dissociation and depression symptoms was also examined to consider posttraumatic neuropsychiatric dysfunction more broadly.

2. Methods and materials

2.1. Participants

Volunteers were recruited as part of a larger, ongoing, multisite longitudinal study of posttraumatic outcomes – the AURORA study (McLean et al., 2019). Participants were recruited from 22 Emergency Departments (EDs) across the United States following trauma exposure. Exposures included motor vehicle collision, physical assault, sexual assault, fall greater than 10 feet, mass casualty incidents, or other plausible exposure to threatened or actual injury, violence, or death. For more details of inclusion and exclusion criteria, please refer to the methodology paper describing the AURORA study (McLean et al., 2019) and the supplement. Structural MRI and psychophysiological assessment were completed within approximately two-weeks of recruitment at one of four locations (McLean Hospital, Emory University, Temple University, or Wayne State University). All participants gave written informed consent as approved by each study site's Institutional Review Board. Trauma-exposed adults ($N = 126$) with complete MRI data at the time of analysis were included in the present study. Twenty-seven participants were excluded from analyses due to noise artifact in FPS data during extinction. Therefore, 99 participants were included in the present analysis ($M = 35.95$ years, $SD = 13.58$ years, range = 18–75; $n = 64$ females; Table 1).

2.2. Self-report measures

The PTSD Checklist for DSM-5 (PCL-5) was used to assess the presence and severity of PTSD symptoms at two- and eight-weeks post-trauma and is scored out of 80 points (Weathers et al., 2013). Note, of participants who provided PCL-5 data at two-weeks post-trauma, 33 participants (33%) scored higher than 32 on the PCL-5, indicative of subacute PTSD. Of participants who provided PCL-5 data at eight-weeks post-trauma, 35 participants (35.4%) scored higher than 32 on the PCL-5 indicative of probable PTSD. Dissociative symptoms were examined with a modified version of the Brief Dissociative Experiences Scale scored out of eight points (DES-B; Dalenberg and Carlson, 2010), see supplement for details. Depression symptoms were assessed with the Patient-Reported Outcomes Measurement Information System (PROMIS) Depression instrument (Pilkonis et al., 2011) which is T-score converted. PTSD, dissociation, and depression symptoms were evaluated for the past 2 weeks at the two-week time point and for the past month at the eight-week time point. Some participants did not provide self-report data; please see the sample description in Supplemental Table 1 for more information. Additionally, the Life Events Checklist (Weathers et al., 2013) was utilized to assess for prior traumatic experiences. Responses were summed to create a composite trauma score and correlated with subcortical GMVs to consider the role of prior traumas on GMV (see supplement).

Table 1
Sample characteristics of included participants (N = 99).

		N (%)	M (SD)
Sex	Male	35 (35.4)	
	Female	64 (64.6)	
Race/Ethnicity	Hispanic	20 (20.2)	
	Non-Hispanic White	39 (39.4)	
	Non-Hispanic Black	35 (35.4)	
	Non-Hispanic Other	5 (5.1)	
Educational Attainment	Some high school	4 (4.0)	
	High school graduate	16 (16.2)	
	GED or equivalent	13 (13.1)	
	Some college, no degree	32 (32.3)	
	Associate degree, technical/ occupational/vocational program	5 (5.1)	
	Associate degree, academic program	6 (6.1)	
	Bachelor's degree	18 (18.2)	
	Master's degree	4 (4.0)	
	Professional school degree	1 (1.0)	
Site	Emory University	7 (7.1)	
	McLean Hospital	51 (51.5)	
	Temple University	18 (18.2)	
	Wayne State University	23 (23.2)	
GMV ROI Proportion of Total ICV	Thalamus	98	0.49 (0.04)
	Amygdala	95	0.11 (0.01)
	Hippocampus	98	0.26 (0.03)
Late Extinction FPS	CS+	98	20.18 (44.97)
	CS-	97	13.83 (43.47)
	(CS+) – (CS-)	96	6.50 (27.28)
PCL-5 Scores	2 weeks post-trauma	89	28.53 (15.42)
	8 weeks post-trauma	86	27.63 (16.68)
Dissociation total Scores	2 weeks post-trauma	91	1.43 (1.68)
	8 weeks post-trauma	88	1.53 (2.0)
PROMIS Depression T-Scores	2 weeks post-trauma	90	54.08 (8.85)
	8 weeks post-trauma	87	55.02 (9.71)

GMV: gray matter volume; ROI: region of interest; ICV: intracranial volume; FPS: fear-potentiated startle; CS: conditioned stimulus.

2.3. MRI acquisition and processing

Anatomical T1-weighted MRI scans were acquired on 3T Siemens MRI systems at four neuroimaging centers (Supplemental Table 2). Image processing was completed at Emory University utilizing standard procedures in fMRIPrep (Esteban et al., 2019), see supplement for details. All segmentations were visually inspected with special attention to individual regions whose volume fell outside ± 1.5 times the interquartile range for the sample. Regional volumes were excluded from analysis if there was a clear segmentation error by Freesurfer (listed by

region in Supplemental Table 1).

2.4. Stimuli and task design

Psychophysiological data were collected within approximately two weeks of trauma exposure using a Pavlovian fear conditioning procedure described in prior reports (Glover et al., 2011; Jovanovic et al., 2012; Norrholm et al., 2011). Briefly, a shape on a computer screen (a blue square; CS+) was repeatedly paired with an aversive unconditioned stimulus (US) (140 psi airblast to the larynx, 250 ms duration). A different shape (a purple triangle; CS-) was never paired with the aversive stimulus. The paradigm included a 108 dB white noise startle probe that elicited the eyeblink startle response. The startle probe was presented during CS+ and CS- trials, and on its own (noise alone [NA] trials) to assess individual baseline startle response. See supplement for further details on the paradigm. Following habituation (see supplement), acquisition consisted of three conditioning blocks with four trials of each type (NA, CS + paired with US, CS-) in each block. Ten minutes after acquisition, the extinction phase consisted of four blocks with four trials of each type (CS+, CS-, NA), wherein the airblast never occurred (20 min in duration). Due to its relevance in the development of PTSD symptoms, the focus of this study was on extinction, thus analyses were limited to late extinction, defined as the last two blocks of extinction.

2.5. Fear-potentiated startle response

FPS was measured using surface electromyography (EMG) of the right orbicularis oculi muscle using a Biopac MP160 physiological recording system (Biopac Systems, Inc. Aero Camino, CA). FPS was defined as the maximal orbicularis oculi contraction 20–200 ms following the startle probe presentation. EMG data were analyzed using MindWare software (MindWare Technologies, Inc.; Gahanna, OH). FPS was calculated by subtracting the average startle magnitude to the noise probe alone from the startle magnitude to each CS in each block of the experiment (Norrholm et al., 2011), see supplement for details. Individuals who had less than 75% useable data as identified during visual inspection were excluded from analyses, as above (Supplemental Table 1).

2.6. Statistical analysis

Statistical analyses were completed using SPSS software (IBM Corporation, version 24, Armonk, NY). Individual multiple regression analyses were completed to assess the relationship between FPS to the CS+ and subcortical GMV in each *a priori* region of interest (i.e., amygdala, hippocampus, and thalamus). Regional volumes were normalized as a proportion of total intracranial volume (ICV) to adjust for potential global ICV differences among participants. GMV for each region was averaged across hemispheres given our lack of *a priori* hypotheses on laterality and the high correlations between hemispheres per region (see supplement). Exploratory post-hoc analyses assessed the relationship with other subcortical regions including bilateral lateral ventricles, globus pallidus, caudate, putamen, and nucleus accumbens.

Second, multiple regression analyses were completed to assess the relationship between FPS during late extinction and subcortical volume on PCL-5 total scores at eight-weeks post-trauma. The regression models (type 3 sums of squares approach) included mean-centered regressors for FPS, GMV, and an FPS by GMV interaction as independent variables with PCL-5, modified DES-B, and PROMIS Depression scores at eight-weeks as the respective dependent variables. FPS and GMV were analyzed as continuous variables. However, to aid in interpretation of the interaction effects, FPS was divided into low and high groupings based on median split where noted. Age, sex, and scan site were included as covariates within the models. We applied a Bonferroni correction for multiple comparisons across the three GMV regions studied at the eight-week timepoint, as this was the primary aim of the study, with a threshold p-value of 0.017. We completed post-hoc regression analyses that included two-week scores as a covariate to determine if observed effects were specific to the eight-week timepoint. Further, supplementary follow-up analyses evaluating interactions at two-weeks post-trauma exposure were completed. Additional exploratory post-hoc analyses investigated the relationship with supplementary subcortical regions at two- and eight-weeks following trauma exposure (Supplemental Tables 4 and 5). Additional exploratory analyses tested interactions with dissociation and depression symptoms.

3. Results

3.1. Associations between GMV and FPS

We first assessed whether GMV related to FPS during late extinction. No significant associations were observed between FPS and GMV in the amygdala, hippocampus, or thalamus (amygdala: t (92) = 0.08, β = 0.01, B = 30.76, 95% CI [-733.94, 795.46], p = 0.936; hippocampus: t (95) = −0.40, β = −0.04, B = −61.77, 95% CI [-366.69, 243.15], p = 0.688; thalamus: t (95) = −0.20, β = −0.02, B = −20.62, 95% CI [-229.46, 188.22], p = 0.845). Exploratory analyses examining the interaction between FPS and nucleus accumbens, caudate, putamen, globus pallidus, and lateral ventricles GMV did not reach significance (Supplemental Table 3).

3.2. Interaction of GMV and FPS on posttraumatic symptoms

We next investigated the effect of GMV and FPS during late extinction on PCL-5 scores eight-weeks following trauma exposure. (Table 2). We observed a significant interaction between thalamus GMV and FPS on PCL-5 scores at eight weeks post-trauma after controlling for multiple comparisons (t(75) = 2.49, β = 0.28, B = 2.90, 95% CI [0.58, 5.22], p = 0.015). No significant main effects of GMV or FPS on PCL-5 scores were observed (GMV: t (75) = −0.99, β = −0.13, B = −51.93, 95% CI [-156.96, 53.10], p = 0.328, *FPS:* t (75) = −0.16, β = −0.02, B = −0.01, 95% CI [-0.09, 0.07], p = 0.870*)*. Both greater thalamic GMV with higher FPS, as well as decreased thalamic GMV with lower FPS during late extinction related to greater PCL-5 scores following trauma exposure (Fig. 1). Follow-up correlation analyses were completed separately for low and high FPS groups, defined by median split, to disentangle the interaction effects. The high FPS group show a non-significant positive correlation (r = 0.22, p = 0.18) while the low FPS group showed a significant negative correlation (r = −0.43, p = 0.010), between thalamic GMV and PCL-5 scores at eight-weeks post-trauma. There was no interaction between amygdala or hippocampus GMV and FPS on eight-week PCL-5 scores (amygdala: t (72) = 1.61, β = 0.19, B = 7.48, 95% CI [-1.76, 16.71], p = 0.111; hippocampus: t (75) = 1.50, β = 0.17, B = 2.98, 95% CI [-0.98, 6.95], p = 0.138) (Table 2).

When two-week PCL-5 scores were included in the eight-week model, the GMV-FPS interaction term lost significance, likely due to the high correlation of PCL-5 scores between timepoints (r = 0.65, p < 0.001). To delve further into these findings, additional analyses focused on the two-week timepoint were undertaken. In brief, a similar interaction between thalamus GMV and FPS on PCL-5 scores two-weeks post-

Table 2
Interaction of subcortical GMV and FPS to the CS+ during late extinction on PCL-5 scores eight-weeks post-trauma.

FPS	Eight Weeks	
	β	t (p)
Amygdala	0.19	1.61 (0.111)
Hippocampus	0.17	1.50 (0.138)
Thalamus	0.28	2.50 **(0.015[a])**

FPS, fear-potentiated startle; CS, conditioned stimulus.
[a] p < 0.05, two-sided test.

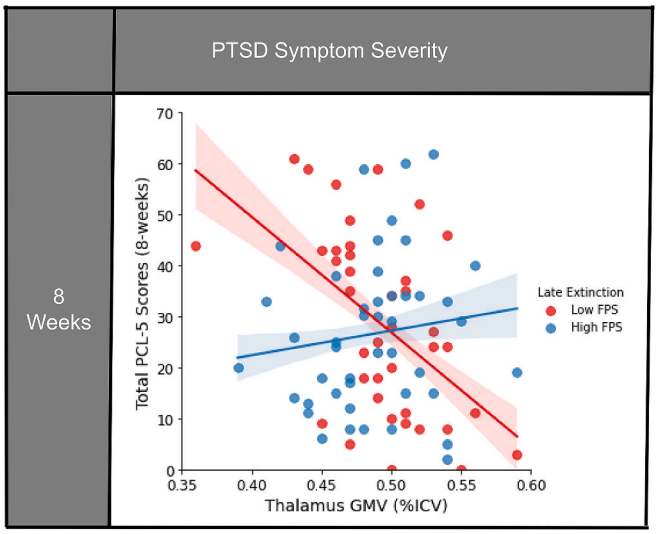

Fig. 1. Significant interaction of FPS to the CS + during late extinction and thalamic GMV on posttraumatic symptom severities at eight-weeks following trauma exposure. FPS is median split here for visual clarity, but analyzed as a continuous variable in the analysis. Confidence intervals shown represent the 68% CI (±1 SE of the regression line). For PCL-5 scores, greater thalamic GMV coupled with higher FPS to danger cue (CS+) during late extinction was associated with greater symptom severity at eight-weeks following trauma exposure; conversely decreased thalamic GMV and low FPS to CS+ during late extinction also related to higher scores post-trauma. FPS: Fear-potentiated startle; GMV: Gray matter volume; ICV: Intracranial volume; PCL-5: PTSD Checklist for DSM-5.

trauma emerged (see supplemental results). Overall, these data suggest that the interaction between thalamic GMV and FPS on PCL-5 scores develops two weeks following trauma exposure, with significant effects persisting weeks later.

Additional analyses involving supplemental subcortical structures demonstrated that at eight weeks post-trauma, an interaction between nucleus accumbens volume and FPS on PCL-5 scores emerged (t (76) = 2.12, $\beta = 0.28$, B = 17.18, 95% CI [1.04, 33.32], $p = 0.037$) as did an interaction between lateral ventricle volume and FPS on PCL-5 scores (t (76) = −2.03, $\beta = -0.32$, B = −0.54, 95% CI [-1.08, −0.01], $p = 0.046$) (Supplemental Table 6).

3.3. Dissociation/depression symptoms at eight-weeks post-trauma

To establish if the above brain-behavior profiles were associated with other posttraumatic outcomes, we also assessed dissociation and depression symptoms using multiple regressions. PCL-5 and modified DES-B scores were highly correlated at each time point (two-week: $r = 0.62$, $p < 0.001$; eight-week: $r = 0.73$, $p < 0.001$). Similar to PCL-5 scores, the thalamic GMV-FPS interaction was associated with modified DES-B scores at eight weeks following trauma exposure (t(77) = 2.54, $\beta = 0.27$, B = 0.34, 95% CI [0.07, 0.61], $p = 0.013$). No significant main effects of GMV or FPS on DES-B scores were observed (GMV: t (77) = −1.36, $\beta = -0.17$, B = −8.11, 95% CI [-20.02, 3.81], $p = 0.179$, FPS: t (77) = −0.56, $\beta = -0.06$, B = 0.00, 95% CI [-0.01, 0.01], $p = 0.576$). Greater thalamic GMV with higher FPS during late extinction and decreased thalamic GMV with lower FPS were both related to higher modified DES-B scores (Fig. 2a).

PCL-5 and PROMIS Depression scores were also highly correlated (two-week: $r = 0.74$, $p = < 0.001$; eight-week: $r = 0.71$, $p = < 0.001$). The interaction between thalamic GMV and FPS during late extinction related to depression severity at eight weeks following trauma (t(76) = 2.40, $\beta = 0.27$, B = 1.75, 95% CI [0.30, 3.20], $p = 0.019$). There were no significant main effects of GMV or FPS on depression scores (GMV: t (76) = −0.95, $\beta = -0.13$, B = −30.58, 95% CI [-94.91, 33.75], p = 0.347, FPS: t (76) = −0.60, $\beta = -0.07$, B = −0.02, 95% CI [-0.07, 0.04], $p = 0.553$). Greater thalamic GMV with higher FPS during late extinction and decreased thalamic GMV with lower FPS were both related to higher depressive symptom severity (Fig. 2b).

These data suggest that the thalamic GMV-FPS interactions may reflect general posttraumatic dysfunction acutely following trauma.

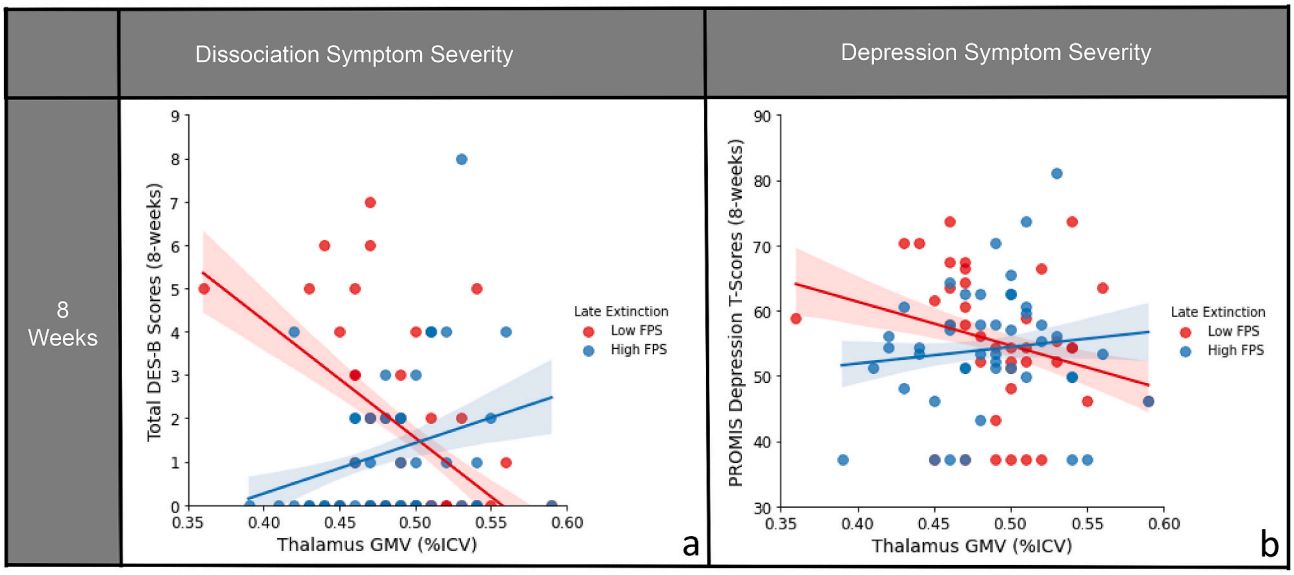

Fig. 2. Interaction of FPS to the CS + during late extinction and thalamic GMV on dissociation and depression symptom severities at eight-weeks following trauma exposure. FPS is median split here for visual clarity, but analyzed as a continuous variable in the analysis. Confidence intervals shown represent the 68% CI (±1 SE of the regression line). For modified DES-B and PROMIS Depression Inventory scores, greater thalamic GMV coupled with higher FPS to danger cue (CS+) during late extinction was associated with greater symptom severity at eight-weeks following trauma exposure; conversely decreased thalamic GMV and low FPS to CS+ during late extinction also related to higher scores post-trauma. A) Interaction of FPS x thalamic GMV predicting modified DES-B scores eight weeks following trauma. B) Interaction of FPS x thalamic GMV predicting PROMIS Depression T-scores eight weeks following trauma. DES-B: Dissociative Experiences Scale- Brief; FPS: Fear-potentiated startle; GMV: Gray matter volume; ICV: Intracranial volume; PROMIS: Patient-Reported Outcomes Measurement Information System.

However, given the high degree of comorbidity of dissociation, depression, and PTSD symptoms, when PCL-5 scores were included as a covariate, the interaction terms were no longer significant (eight-week modified DES-B: (t (74) = 1.03, β = 0.08, B = 0.10, 95% CI [-0.09, 0.30], p = 0.304; eight-week PROMIS Depression: (t (73) = 0.75, β = 0.06, B = 0.42, 95% CI [-0.70, 1.53], p = 0.458).

3.4. Assessing FPS stability throughout extinction

As a post-hoc analysis, we sought to determine, among participants with elevated PCL-5 scores, defined by a PCL-5 score of greater than 32, if low FPS in late extinction was reflective of enhanced learning (a change over the course of extinction) or a persistent behavioral response. Only the high FPS group had a significant intercept term for FPS, (High: t (14) = 3.88, p = 0.002; Low: t (16) = −0.76, p = 0.46), indicating only the high FPS group potentiated relative to baseline startle, consistent with fear learning. Individuals with low FPS during late extinction were persistently low throughout extinction, while those with high FPS during late extinction were also persistently increased (see supplement). Most critically, low FPS reactivity during late extinction was a marker of low initial psychophysiological reactivity maintained throughout extinction.

4. Discussion

We investigated subcortical GMV and extinction-related FPS in recently traumatized individuals to identify brain-behavior relationships associated with acute PTSD symptom development. Interactions between thalamic GMV and FPS during late extinction showed a significant effect on PTSD, dissociation, and depression symptom severity at two- and eight-weeks following trauma exposure. While FPS and GMV appear to be independent of one another during the acute posttraumatic phase, these measures in combination were informative of susceptibility to posttraumatic dysfunction. Among participants experiencing posttraumatic stress symptoms, two distinct brain-behavior profiles emerged, indicative that neither GMV nor FPS data alone sufficiently characterized the risk for posttraumatic symptom development.

Our findings that subcortical GMV did not vary with autonomic reactivity are inconsistent with prior human functional (Cheng et al., 2006; Harnett et al., 2015; Knight et al., 2004) and structural (Hartley et al., 2011) MRI research demonstrating relationships between the amygdala and hippocampus and skin conductance responses (SCRs) during fear acquisition (Pohlack et al., 2012). Although both SCR and FPS index psychophysiological arousal, they have differing neural substrates that may lead to different brain-behavior relationships (Abend et al., 2020; Glover et al., 2011; Lindner et al., 2015; Young et al., 2018), potentially underlying the discrepant findings. Additionally, we focused on extinction learning only, which involves new learning reliant on related, but distinct, neural mechanisms (Phelps et al., 2004).

While subcortical GMVs were independent of FPS during late extinction, an interaction between thalamic GMV and FPS was related to future (i.e., eight-week) PTSD symptom severity. Two distinct brain-behavior phenotypes were associated with greater PTSD symptoms following trauma: 1) individuals with greater thalamic GMV in combination with higher FPS, and 2) individuals with decreased thalamic GMV in combination with lower FPS. We speculate that the group high GMV/FPS may relate to the 'classical' concept of PTSD symptomatology, namely patients unable to extinguish the fear response during safety. Conversely, the group with low GMV/FPS may represent individuals with consistently blunted behavioral responses (e.g., a more emotionally numb or avoidant subtype). These results highlight the utility of multimodal approaches to better characterize individual PTSD phenotypes and to potentially inform optimal preventive/treatment interventions.

To contextualize these findings, prior translational evidence links thalamic activity and FPS responses to threat cues and PTSD (Davis, 2006; Lindner et al., 2015). The thalamus integrates sensory signals and projects directly and indirectly to the medial prefrontal cortex (mPFC) (Lee et al., 2019; Lindner et al., 2015; Ramanathan et al., 2018; Ramanathan and Maren, 2019), an area central to the formation of extinction memories (Mitchell, 2015; Ouhaz et al., 2018). Importantly, several thalamic subregions are heavily implicated in extinction circuitry. The nucleus reuniens is a key site where mPFC signals converge to regulate the suppression or retrieval of threat memories (Giustino and Maren, 2015). It is also linked to sleep-related memory consolidation (Hauer et al., 2019), with sleep disruptions thought to significantly contribute to the development of PTSD symptoms (Neylan et al., 2020). Additionally, the dorsal medial thalamus is tied to extinction learning. When dorsal medial thalamic projections to the amygdala are suppressed, extinction is promoted, outlining the critical function this region plays in extinction (Ramanathan et al., 2018). Our findings could point to hypertrophy or atrophy of either of these subregions, leading to dysfunction in the circuitry underlying extinction learning. While the T1w imaging used here accurately segments the thalamus en bloc, further dissection requires diffusion tensor imaging (Battistella et al., 2017) or 7T imaging (Xiao et al., 2016). As advanced methodologies become validated, further subsegmentation of the thalamus to delineate its effects on posttraumatic outcomes is warranted.

Interestingly, the GMV-FPS interaction also predicted dissociation and depression symptom severity. PTSD is often comorbid with both dissociation (Stein et al., 2014) and depression (Bleich et al., 1997; Breslau et al., 2000; Shalev et al., 1998). Due to its role in sensory integration and relay, the thalamus is heavily implicated in dissociative disorders (Krause-Utz et al., 2017), with differences observed in both structural and perfusion studies (Schlumpf et al., 2014; Shucard et al., 2012). Additionally, volumetric data shows mixed results with both greater and smaller thalamic volumes associated with depression (Ancelin et al., 2019; Young et al., 2008) compared to controls. Our data demonstrate both groups at risk for depression and dissociation symptoms following trauma, illustrating the importance of multimodal analysis when considering morphometric data in heterogeneous and complicated clinical populations.

Our findings should be considered in light of several limitations. While the comorbidity in our sample is quite common in the clinical realm and is representative of a naturalistic sample, it limited our ability to examine each symptom cluster in isolation. Thus, while our findings highlight brain-behavior interactions in relation to general posttraumatic dysfunction, we are unable to identify specific neural substrates unique to PTSD, or other related disorder, symptom development. Second, the sample included relatively low PTSD severity, as reported on the PCL-5, which may limit extrapolation to a more clinically severe population. Additionally, the dissociation scale used included only two items from the DES-B, thus likely not capturing all volunteers with dissociation symptoms. Lastly, the present study did not include a non-traumatized control group to assess whether these brain-behavior relationships are only observed in the early aftermath of trauma or may also be observed in the general population.

5. Conclusion

In this sample of recently traumatized individuals, subcortical GMV and FPS during late extinction interacted to significantly relate to broad posttraumatic neuropsychiatric symptoms (i.e., PTSD, dissociation, and depression) at eight-weeks following trauma exposure. Our observation of high posttraumatic symptoms in both low GMV/FPS and high GMV/FPS groups suggest different neural mechanisms mediate different subtypes of posttraumatic sequalae. An appreciation for the complex interplay of brain structure and psychophysiology may help to inform effective, individualized interventions for those at risk for adverse outcomes following trauma.

Declaration of competing 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.jpsychires.2021.07.023.

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