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Autonomic responses to fear conditioning among women with PTSD and dissociation

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Abstract

Background: Individuals with posttraumatic stress disorder (PTSD) demonstrate alterations in autonomic responses to fear conditioning, such as exaggerated startle and poor fear inhibition. However, there is a paucity of research on fear conditioning among individuals with PTSD and dissociative symptoms, which represents 10–30% of those with PTSD. The current study used a fear-potentiated startle (FPS) conditioning paradigm to examine autonomic responses among women with PTSD and a range of dissociative symptoms.

Methods: Participants included 39 women with PTSD and dissociation, and 53 women with PTSD with unknown levels of dissociation. The FPS paradigm consisted of conditioned stimuli associated and not associated with an aversive unconditioned stimulus. FPS response (eyeblink startle), electrocardiogram (ECG), and skin conductance response (SCR) were collected during the FPS paradigm.

Results: Compared to the PTSD-unknown dissociation sample, the PTSD-dissociation sample demonstrated significantly lower FPS during the last block of conditioning. Among the PTSD-dissociation sample, higher dissociation scores were associated with decreased FPS and SCR, and higher respiratory sinus arrhythmia (derived from ECG).

Conclusions: Results suggest that autonomic responses to fear conditioning differ depending on the presence and severity of dissociative symptoms. Given that treatment response may differ depending on dissociative symptoms, it is important to understand the mechanisms that underlie different subtypes of PTSD and that may affect treatment response and outcome.

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1 | INTRODUCTION

Individuals with posttraumatic stress disorder (PTSD) demonstrate alterations in autonomic responses to fear learning, such as exaggerated startle and poor fear inhibition to safe stimuli. The etiology of PTSD may have basis in classical conditioning principles, such that an aversive unconditioned stimulus (US; e.g., assault) is paired with a conditioned stimulus (CS; e.g., nearby sound) and results in a conditioned response (CR; e.g., fear and startle response; Davis, 1990). Previous research has demonstrated that individuals with PTSD exhibit greater fear-potentiated startle (FPS; eyeblink startle response to CSs) than those without PTSD symptoms (Grillon & Morgan, 1999; Jovanovic et al., 2009, 2010; Sijbrandij, Engelhard, Lommen, Leer, & Baas, 2013). Despite the preponderance of research on fear learning in PTSD, no prior studies have examined these phenomena among individuals with both PTSD and dissociative symptoms. Given prior research demonstrating important neural differences among those with dissociation, the current study sought to understand how the presence of dissociative symptoms may alter fear-learning responses among individuals with PTSD.

Neuroimaging research has provided insight into the neural underpinnings of fear-learning processes. During typical fear-learning, the amygdala becomes activated, and this activity is subsequently suppressed by activation of the ventromedial prefrontal cortex (vmPFC), representing fear inhibition (Quirk, Garcia & González-Lima, 2006; Stanek, Walker, & Davis, 2000). Among individuals with PTSD, this process is often dysregulated in one of two ways, depending on the presence of co-occurring dissociative symptoms. Dissociative symptoms in this context refer to pathological feelings of detachment from one's thoughts, feelings, body, sense of self, or surroundings (i.e., depersonalization and derealization; Holmes et al., 2005). In symptom provocation paradigms, those with PTSD but without dissociative symptoms often report feeling hyperaroused. This is evidenced by increased heart rate and amygdala activation, and decreased vmPFC activation compared to control participants, suggesting under-regulation of fearful/emotional responding (Hopper, Frewen, van der Kolk, & Lanius, 2007; Lanius, Williamson, Boksman et al., 2002; Robinson, Krimsky, Lieberman et al., 2014). In contrast, individuals who have PTSD with dissociative symptoms are more likely to exhibit increased vmPFC activity, decreased amygdala activation, and either no change in or decreased heart rate (Hopper et al., 2007; Lanius, Williamson, Boksman et al., 2002; Robinson, Krimsky, Lieberman et al., 2014). These findings are suggestive of over-regulation in emotional responding among individuals with PTSD and co-occurring dissociation.

Similarly, research has examined the peripheral physiology of dissociation as related to stressful cues, and has generally found it to be associated with decreased autonomic arousal and reactivity among trauma-exposed individuals with varying levels of PTSD symptoms (e.g., D'Andrea, Pole, DePierro, Freed, & Wallace, 2013; Griffin, Resick, & Mechanic,

1997; however see also Kaufman et al., 2002 for alternate results). For example, Griffin et al. (1997) found that female sexual assault survivors with high levels of dissociation demonstrated decreased skin conductance and heart rate compared to those with low levels of dissociation (both at baseline and when discussing the assault). Similar findings were reported by D'Andrea et al. (2013), such that symptoms of dissociation were associated with decreased skin conductance among trauma-exposed college students. Given these findings regarding PTSD with co-occurring dissociation, as well as latent class and genetic studies demonstrating its distinction from PTSD without dissociation (Stein et al., 2013; Wolf et al., 2012, 2014), it follows that individuals with PTSD and dissociative symptoms represent a distinct subtype of those suffering with PTSD. Despite this, there is a paucity of research on fear conditioning and its physiological correlates among individuals with PTSD and co-occurring dissociation.

It is well established that fear conditioning is central to the development and maintenance of PTSD, and extinction of fear is a critical target among empirically supported treatments for PTSD (e.g., prolonged exposure, cognitive processing therapy; Foa, Hembree, & Rothbaum, 2007; Resick, Monson, & Chard, 2016). It is therefore imperative to achieve a thorough understanding of these processes among individuals who experience PTSD with co-occurring dissociation because over-regulation of emotion may interfere with the emotional engagement necessary for proper extinction. This need is further demonstrated by the lack of clarity regarding treatment outcomes for those with PTSD and dissociation (e.g., Lanius et al., 2012; Wolf, Lunney, & Schnurr, 2016). Understanding fear-conditioning response among individuals with PTSD and dissociation may help elucidate underlying mechanisms that explain treatment outcomes.

To address this gap, the current study examined autonomic responses relevant to fear conditioning in a fear-potentiated startle (FPS) paradigm among individuals with PTSD and dissociative symptoms compared to those with PTSD and unknown levels of dissociation. Most PTSD research has been limited in not assessing dissociation and thus having mixed samples; therefore, the current study provides a more challenging comparison group but one that is more comparable to other PTSD studies. Given previous evidence of over-regulation in patients with dissociation, we hypothesized that: (a) compared to the PTSD-unknown dissociation sample, the PTSD-dissociation sample would demonstrate decreased startle response, heart rate (HR), and skin conductance response (SCR), and higher respiratory sinus arrhythmia (RSA); (b) within the PTSD-dissociation sample, higher levels of self-reported dissociation would be associated with lower eyeblink startle response during fear conditioning, as well as lower HR and SCR and higher RSA; (c) RSA would mediate the association between dissociative symptoms and startle reactivity/SCR among the PTSD-dissociation sample.

2 | METHODS

2.1 | Participants

The PTSD-dissociation sample was comprised of two smaller samples of women with PTSD and dissociation. One sample consisted of 20 women ($M_{age} = 39.75$) seeking treatment from a psychiatric hospital in Belmont, MA. All participants endorsed significant symptoms

of PTSD and dissociation determined by clinical interview and self-report. The replication sample consisted of 19 women ($M_{age} = 37.68$) recruited from a general medical hospital in Atlanta, GA as part of the Grady Trauma Project (GTP; see Gillespie et al., 2009). These participants endorsed significant symptoms of PTSD as determined by clinical interview, and self-reported dissociation symptoms. Given that these two samples did not significantly differ on the main outcome variables (e.g., startle reactivity and RSA), they were combined. Thus, the total PTSD-dissociation sample consisted of 39 women ($M_{age} = 38.74$) with trauma histories, PTSD diagnoses, and significant dissociative symptoms.

The PTSD-unknown dissociation sample consisted of 53 women ($M_{age} = 38.79$) recruited from a general medical hospital in Atlanta, GA as part of the GTP. These participants endorsed significant symptoms of PTSD as determined by self-report, including significant re-experiencing symptoms. Given that this was a naturalistic PTSD sample without a focused dissociation interview, participants had unknown levels of dissociation. This resulted in a stronger comparison to the PTSD-dissociation sample because some participants may have had dissociative symptoms, thus increasing the threshold for observing significant group differences.

Both sites obtained written informed consent from participants, administered the same FPS paradigm, and were granted approval by their respective Institutional Review Boards. See Table 1 for demographics and childhood trauma exposure among each sample.

3 | MEASURES

3.1 | Trauma and PTSD

3.1.1 | Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994)—The CTQ is a 25-item self-report measure used to evaluate the frequency of childhood abuse and neglect. There are five subscales measuring frequency of sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect. The CTQ has been shown to have moderate to high internal consistency in a variety of clinical and nonclinical populations, as well as good convergent and construct validity (Bernstein et al., 1994).

3.1.2 | Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013a)—The CAPS-5 is a clinician-administered interview designed to assess the frequency and severity of 20 *DSM-5* PTSD symptoms, as well as diagnostic status (American Psychiatric Association, 2013). Of particular importance for our study, the CAPS-5 includes assessment for a dissociative subtype of PTSD using items probing for experiences of depersonalization and derealization. The CAPS-5 has demonstrated strong internal consistency (Cronbach's $\alpha = 0.94$), interrater reliability ($\kappa = 0.78$ to 1.00), test-retest reliability, convergent validity with other established PTSD measures, and good discriminant validity with measures of anxiety, depression, somatization, functional impairment, psychopathy, and alcohol abuse (Weathers et al., 2017). The CAPS-5 was administered to the PTSD-dissociation psychiatric sample.

3.1.3 | Modified PTSD symptom scale (PSS; Falssetti, Resnick, Resick, & Kilpatrick, 1993)—The modified PTSD Symptom Scale (PSS) is a 17-item self-report

measure of *DSM-III-R* PTSD symptoms experienced over the past 2 weeks. The PSS has demonstrated strong internal consistency (Cronbach's $\alpha = 0.94$), high test-retest reliability, and good concurrent validity (Foa, Riggs, Dancu, & Rothbaum, 1993). The PSS was administered to the PTSD-dissociation general hospital sample, as well as the PTSD-unknown dissociation sample.

3.1.4 | PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013b)—The PCL-5 is a 20-item self-report measure of PTSD symptoms that corresponds to the four *DSM-5* symptom clusters. These clusters include: Intrusion (Cluster B; 5 items), Avoidance (Cluster C; 2 items), Negative Alterations in Cognition and Mood (Cluster D; 7 items), and Alterations in Arousal and Reactivity (Cluster E; 6 items). The PCL-5 was administered to the PTSD-dissociation psychiatric sample.

3.2 | Dissociation

3.2.1 | Structured Clinical Interview for DSM-IV dissociative Disorders-Revised (SCID-D-R; Steinberg, 1994)—The SCID-D-R is a semistructured interview considered to be the standard in diagnostic assessment for each of the *DSM-IV* dissociative disorders. In terms of psychometric properties, the SCID-D-R has demonstrated good to excellent test-retest reliability over a 7-day period, as well as good to excellent discriminant validity for each of the dissociative symptom clusters and each of the dissociative disorders (Steinberg, 1994). The SCID-D-R was administered to the PTSD-dissociation psychiatric sample.

3.2.2 | Multidimensional Inventory of Dissociation (MID; Dell, 2006)—The MID is a 218-item self-report measure designed to assess pathological dissociation and diagnose dissociative disorders. The MID has demonstrated excellent internal consistency (Cronbach's $\alpha = 0.98$) and test-retest reliability over 4 to 8 weeks (Dell, 2006). In addition, it shows excellent construct validity with standardized measures of traumatic stress and discriminative validity with the SCID-D-R. The MID was administered to the PTSD-dissociation psychiatric sample.

3.2.3 | Multiscale Dissociation Inventory (MDI; Briere, 2002)—The MDI is a 30-item self-report measure of dissociative symptoms. The MDI has been found to have good psychometric qualities in both the normative and validation samples, with Cronbach's $\alpha = 0.74$ to 0.96 (Briere, 2002). The MDI was administered to the PTSD-dissociation general hospital sample.

3.3 | FPS paradigm and equipment

The FPS paradigm was based on classical conditioning principles, whereby an aversive US (140 psi airblast, 250 ms duration) was repeatedly paired with a shape (e.g., a blue square; CS+)—a danger signal, whereas a different shape, (e.g., a purple triangle), was never paired with the aversive stimulus (safety signal; CS−). The paradigm included a 108-dB startle probe that elicited the eyeblink acoustic 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. The startle probe was presented 6 s after initiation of the CS and

was followed by the US 0.5 s later. The acquisition phase of the paradigm consisted of one habituation block where no airblasts were delivered, immediately followed by three conditioning blocks with four trials of each type (NA, CS+, CS-) in each block (20 min in duration). The intertrial interval was jittered between 9 and 22 s. See Figure 1 for an overview of the fear acquisition phase of the FPS paradigm. Participants also completed an extinction phase of the paradigm in which the airblast never occurs (20 min in duration; 10 min after the end of acquisition). Given the current study's focus on fear learning specifically, extinction results are not presented.

Biopac MP150 for Windows (Biopac Systems, Inc.; Goleta, CA) was used to collect psychophysiological data. Experimental stimuli were presented using SuperLab 5.0 for Windows (Cedrus, Inc.; San Pedro, CA). The startle response was measured via electromyography (EMG) of the right orbicularis oculi muscle and was identified as the maximum amplitude of the eyeblink muscle contraction occurring between 20 and 200 ms after the startle probe was presented. Two pregelled disposable Ag/AgCl electrodes were positioned approximately 1cm under the pupil and 1cm below the lateral canthus. All impedances were less than 6 k Ω . EMG activity was acquired at a sampling rate of 1 kHz, amplified and digitized using the EMG module of the Biopac system. The startle probe was a 108-dB 40-ms burst of broadband noise with a near instantaneous rise delivered through headphones. Heart rate and SCR were measured using two pregelled disposable Ag/AgCl electrodes each and acquired at a sampling rate of 1 kHz, amplified and digitized using the Biopac system. Heart rate electrodes were pregelled with electrolyte gel and placed on the left forearm and right clavicle, whereas SCR electrodes were pregelled with isotonic paste and placed on the hypothenar surface of the nondominant hand.

3.4 | Physiological data cleaning and calculation

Outcome variables were processed for analysis using MindWare software (MindWare Technologies, Inc.; Gahanna, OH). Screening of eyeblinks involved visually inspecting EMG data for double blinks and other artifacts. When necessary, segments of EMG data without an identifiable eyeblink were removed. FPS in each block was calculated using a difference score (peak startle magnitude in the presence of a CS for that block – peak startle magnitude to the NA trials for that block; Jovanovic et al., 2005). Thus, there were four CS +, four CS –, and four NA trials in each block. SCR was visually inspected for artifacts and trials without identifiable SCRs were removed. SCR was calculated using a difference score (average SC during 3–6 s after CS onset – average SC during the second prior to stimulus onset). As in our previous studies, we used block 2 and 3 of the fear-conditioning session to define “late acquisition” to capture the learned fear response (Jovanovic et al., 2013). For FPS and SCR, this combined variable (an average of blocks 2 and 3) was used in some analyses in addition to examining each block separately.

To obtain HR and RSA, MindWare identifies ECG R-peaks and R-R intervals (the time between heartbeats), and detects improbable R-peaks, which can then be manually inspected and corrected. Settings for high and low frequency bands were set to 0.15–0.40 Hz based upon standard recommendations for RSA data (Berntson et al., 1997). Given our interest in testing differential autonomic responses to fear conditioning (rather than baseline

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differences), we used a change score for RSA. Change in RSA was obtained by subtracting the average RSA value for minute one of habituation (i.e., baseline—no stimuli present) from the average RSA value from the last minute of the fear acquisition session. HR and RSA values were also calculated for each of the three conditioning blocks.

3.5 | Statistical analyses

For Hypothesis 1 (group differences), two three-way mixed analyses of variance (ANOVAs) were used to examine the between-groups factor of Group (PTSD-unknown dissociation vs. PTSD-dissociation) and within-subjects factors of CS-type (CS+ vs. CS-) and Block (3) for SCR and FPS. Two two-way ANOVAs were used to examine Group (PTSD-unknown dissociation vs. PTSD-dissociation) by Block (3) differences for HR and RSA (CS-type was not examined given that HR and RSA were not tied to specific stimuli but were captured continuously throughout the paradigm). A Sidak correction was used for multiple comparisons.

For Hypothesis 2 (bivariate analyses with self-reported dissociation), the two smaller PTSD-dissociation samples were analyzed separately since they were administered two different measures of dissociation (MID vs. MDI). Given the small sample sizes and limitations of interpreting such analyses with p values (e.g., Kline, 2004; Sullivan & Feinn, 2012), we focused our results on the strength of the effects and interpreted $r = 0.10$ as small, $r = 0.30$ as medium, and $r = 0.50$ as large (Cohen, 1992).

For Hypothesis 3 (mediation by RSA), a nonparametric resampling approach (bootstrapping; Preacher & Hayes, 2004) was used to assist in determining the effects of RSA change on the association between dissociation and FPS/SCR. This procedure is preferable because it accounts for small sample size and potential abnormality in variable distribution, and because it provides a confidence interval (CI) for the point estimates.

4 | RESULTS

The PTSD-unknown dissociation and PTSD-dissociation samples both demonstrated significant levels of PTSD symptoms as indexed by the PSS and PCL-5. Specifically, the mean PSS score was 34.85 ($SD = 7.69$) in the PTSD-unknown dissociation sample and 24.68 ($SD = 7.92$) in the PTSD-dissociation general hospital sample. The suggested PSS cutoff score for PTSD is 14; thus, both samples demonstrated clinically significant symptoms of PTSD. The mean PCL-5 score was 46.41 ($SD = 15.35$) in the PTSD-dissociation psychiatric sample. The suggested PCL-5 cutoff score for PTSD is 33; thus, the participants in this sample also demonstrated clinically significant PTSD symptoms. To compare the groups on PTSD symptom severity, we also calculated a percentage of PTSD symptoms endorsed by dividing each individual severity score by the total possible score for that measure. The average percentages were 68% in the PTSD-unknown dissociation sample and 55% in the PTSD-dissociation sample. A one-way ANOVA indicated that this difference was significant, $F(1,93) = 15.17$, $p < 0.001$.

Hypothesis 1. Group differences

To test our first set of hypotheses, we ran two separate three-way mixed ANOVAs to examine the between-groups factor of Group (PTSD-unknown dissociation vs. PTSD-dissociation) and within-subjects factors of CS-type (CS+ vs. CS-) and Block (3)—one for SCR and one for FPS. For SCR, there were significant main effects of CS-type, $F[1,80] = 9.18, p = 0.003$ and Block, $F[1,80] = 7.26, p = 0.009$, but the interaction effects were not significant.

For FPS, there were significant main effects of CS-type, $F[1,88] = 12.34, p = 0.001$, and Block, $F[1,88] = 7.25, p = 0.008$, a significant two-way interaction of CS-type by Group, $F[1,88] = 5.69, p = 0.019$, and a significant three-way interaction, $F[1,88] = 4.47, p = 0.037$. For an illustration of the three-way interaction (Group by Block shown for each CS), see Figure 2. To further probe these effects and determine where differences were significant between groups, pairwise comparisons were examined on the estimated marginal means within the model. As demonstrated in Figure 3, FPS to the CS+ appeared to be lower in the PTSD-dissociation group compared to the PTSD-unknown dissociation sample during block 3 but this was not statistically significant, $M_{diff} = 32.86, t(1,88) = -1.78, p = 0.079, d = 0.384$, Sidak-adjusted. Separate post-hoc repeated measures analyses were conducted in each sample for the CS+ and indicated a significant quadratic effect of block for the CS+ in the PTSD-dissociation sample, $F[1,37] = 11.12, p = 0.002$ and no effect in the PTSD-unknown dissociation sample. Together these data suggest that the PTSD-dissociation sample demonstrated a more rapid suppression of FPS to the CS+ with repeated fear conditioning blocks compared to the PTSD-unknown dissociation sample.

For HR and RSA, average scores in each block were used (not tied to stimuli). With respect to HR, a group (2) by block (3) repeated measures ANOVA revealed a significant main effect of block, $F[1,83] = 5.80, p = 0.007$ and a significant interaction, $F[1,83] = 4.42, p = 0.039$; Figure 4. Pairwise comparisons did not reveal significant differences between groups. Separate post-hoc repeated measures analyses were conducted in each sample for HR and indicated a significant quadratic effect of block for HR in the PTSD-dissociation sample, $F[1,39] = 10.23, p = 0.003$ and a significant linear effect in the PTSD-unknown dissociation sample, $F[1,44] = 13.29, p = 0.001$. Overall, these results suggest that HR accelerated in the PTSD-unknown dissociation sample, whereas initially, it decelerated and then rebounded in the PTSD-dissociation sample. With respect to RSA, a group (2) by block (3) ANOVA revealed a near-significant main effect of block, $F[1,83] = 3.95, p = 0.050$. Interaction effects and follow-up analyses were not significant.

Hypothesis 2. Bivariate analyses with self-reported dissociation

4.1 | Dissociation and physiology among the psychiatric sample

Consistent with our first hypothesis, higher levels of dissociation indexed by the MID were associated with lower startle responding and greater increase in parasympathetic activation as indicated by medium effects sizes (see Table 2). No associations were observed between MID and HR with medium or greater effects. Contrary to hypotheses, all MID subscales were positively associated with SCR to the CS+ and CS- during late acquisition (medium-effect sizes), suggesting that greater dissociation was associated with higher levels of sympathetic response to both the danger and safety signal in this sample.

4.2 | Dissociation and physiology among the general hospital sample

Among the general hospital sample, higher levels of dissociation were associated with lower startle responding and decreased sympathetic activation (both SCR and HR), as well as a greater increase in parasympathetic activation as indicated by medium-effect sizes (see Table 3).

Hypothesis 3. Mediation by RSA

To test our hypothesis that increases in RSA mediated the relationship between dissociation and FPS/SCR, we conducted mediation analyses with each of the PTSD-dissociation samples (given that they completed different measures of dissociation). The confidence interval of the indirect effect of RSA change included zero in both samples for both FPS and SCR, suggesting that RSA change did not mediate the relation between dissociation (MID mean or MDI total) and FPS or SCR during late acquisition (blocks 2 and 3).

5 | DISCUSSION

The current study examined autonomic responses to fear conditioning among women with PTSD and dissociation. Results suggest that individuals with PTSD and dissociation exhibited a differential pattern of autonomic response as compared to a general PTSD sample. In addition, higher self-reported dissociation was associated with decreased startle response (FPS) and SCR (in one PTSD-dissociation sample), and higher RSA.

Regarding our first hypothesis, differential response to fear conditioning emerged for women with PTSD-dissociation compared to the PTSD-unknown dissociation sample. The finding that FPS to the CS+ was lower among those with PTSD-dissociation is consistent with prior research demonstrating blunted physiological responding among individuals with significant dissociative symptoms (e.g., D'Andrea et al., 2013; Ebner-Priemer et al., 2005, 2009). Given that groups did not differ significantly in early phases of conditioning, it may be that individuals with PTSD and dissociation have similar initial responses to fearful stimuli, but that they quickly suppress this response, consistent with hypotheses of increased top-down regulation in dissociation (whereas those without dissociation are not as able to rapidly regulate the fear response). Our findings regarding HR indicated that sympathetic activity rose steadily in the PTSD-unknown dissociation sample, whereas in the PTSD-dissociation sample it appeared to decrease and then rebound (as evidenced by linear and quadratic effects, respectively). This may suggest that individuals with PTSD and dissociation demonstrate a differential sympathetic response pattern due to ineffective over-regulation. For example, while they initially suppress HR in block 2, they are not able to sustain this effect and HR rebounds in block 3. Future research is needed to replicate this finding and determine whether or not this has maladaptive consequences for fear learning.

Our second hypothesis was partially supported, such that higher levels of dissociation were associated with lower FPS, SCR, and HR (but only in one PTSD-dissociation sample), and higher RSA during the FPS paradigm. This is consistent with prior research demonstrating that dissociation is associated with blunted sympathetic responding (e.g., D'Andrea et al., 2013; Ebner-Priemer et al., 2005, 2009; Griffin et al., 1997), and contributes vital

information about how individuals with dissociation may respond differently to fear conditioning. An unexpected finding was that SCR to the CS+ in the psychiatric sample was positively related to FPS to the CS-, which is considered a safety signal because it is never paired with the aversive US. Although this finding may be spurious, it may also suggest that dissociation is related to worse safety signal learning and thus greater startle responding to nonthreatening stimuli and stimulus generalization. Future research will be needed to determine if this is relevant to individuals with dissociation or if it was merely an arbitrary effect in the current study. Given the known role of RSA as a parasympathetic nervous system measure of vagal regulation, our results also suggest that dissociation was related to a greater tendency to regulate fear and physiological reactivity in our study, which is consistent with prior research (e.g., D'Andrea et al., 2013; Lanius et al., 2002). It is important to note, however, that sample sizes were small and results focused on effect size rather than significance level as recommended in prior research (e.g., Kline, 2004; Sullivan & Feinn, 2012).

Our third hypothesis was not supported, such that change in RSA did not mediate the associations between self-reported dissociation and FPS/SCR. One potential explanation for this finding is that dissociation does not lead to greater parasympathetic nervous system (PNS) activation (i.e., RSA) and/or that PNS activation is not implicated in the fear-conditioning response. However, prior literature suggests that autonomic regulation does have a pertinent role in both of these phenomena (e.g., D'Andrea et al., 2013; Pappens et al., 2014). This is further supported by the correlations we observed between dissociation and RSA. It is therefore more likely that methodological aspects of our study precluded us from observing an effect. For example, measuring RSA during the FPS paradigm when multiple CSs are presented or having limited RSA epochs from which to measure could have disrupted our ability to observe a connection between RSA and FPS, as well as small sample sizes of the individual PTSD-dissociation samples. Future research is needed to determine if RSA is indeed a mediator between self-reported dissociation and FPS/SCR, or if alternative neural circuit mechanisms are occurring.

The current study may have clinical implications given that fear conditioning models play a central role in treatments for individuals with PTSD (e.g., extinction learning in exposure therapy). Prior research on treatment outcomes among individuals with PTSD and dissociation has been mixed. For example, several studies have demonstrated that individuals with co-occurring dissociation have worse PTSD treatment outcomes than those without dissociation (Bae, Kim, & Park, 2016; Cloitre, Petkova, Wang, & Lu Lassell, 2012; Kleindienst et al., 2011, 2016; for a review see Lanius et al., 2012). Given that FPS appeared to be lower among the PTSD-dissociation sample in our study, this may suggest that individuals with dissociation experience blunted fear learning that impairs their progress in treatment (e.g., if proper fear learning doesn't take place, neither will extinction). Relatedly, our finding that SCR to the danger signal was positively related to FPS to the safety signal may suggest that inaccurate fear learning (low FPS) led to impaired safety perception. This would support the notion that decreased arousal associated with dissociation is maladaptive because it impairs proper fear and safety signal learning. However, a study by Wolf et al. (2016) suggested that treatment responses were similar for those with PTSD regardless of the dissociation status, though they did observe a small effect of dissociation. More research

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is needed to probe whether notable differences exist in treatment outcomes. Perhaps even more important, additional research is needed to elucidate the underlying mechanisms of change. For example, if individuals with PTSD and dissociation have blunted fear expression (which would presumably affect treatment response via disengagement during exposure therapy), but do not differ in their response to treatment, then what other mechanisms are working to confer symptom improvement?

Strengths of the current study include the analysis of autonomic response across multiple physiological measures, as well as the inclusion of several aspects of dissociation. In addition, the inclusion of two independent samples with the same FPS paradigm and PTSD showed that the results were replicated in a second sample. However, there are noteworthy limitations. First, not all participants completed the same measure of dissociation. Despite this, the two samples enriched for PTSD with dissociation did not differ on FPS or RSA variables and were, therefore, combined when compared to a broader PTSD sample. The community PTSD-unknown dissociation sample did not complete a specific measure of dissociation and thus we cannot say with certainty that no participant in that sample experienced significant dissociation. Most studies that use PTSD samples do not assess for dissociation and likely include mixed samples; however, those that do assess dissociation have found that 10–30% of individuals with PTSD have significant dissociation (Armour, Elkli, Lauterbach, & Elhai, 2014; Blevins, Weathers, & Witte, 2014; Stein et al., 2013; Wolf et al., 2012). This makes for a more challenging comparison group in terms of examining differences, but one which may be more meaningful in comparing our PTSD-dissociation sample to the prior PTSD literature. Thus, some of our results may have reached significance if we were able to screen out anyone with dissociation symptoms in the PTSD-unknown dissociation sample. Future studies would benefit from the administration of a common dissociation measure and our group is currently working on such an effort. Another limitation is that the current samples included only women. While this helped to improve homogeneity in our analyses, it will be important to test study hypotheses among men with PTSD and dissociation. Finally, the current study is limited in the racial distribution of its samples. The PTSD-unknown dissociation sample and the PTSD-dissociation general hospital sample were both comprised primarily of African American individuals, whereas the PTSD-dissociation psychiatric sample was comprised primarily of Caucasian individuals. Thus, race is a group confound in this study that precludes us from including it as a covariate (i.e., all group difference variance would be accounted for). In future research we aim to include more diverse samples to accurately investigate racial differences. Despite this limitation, given that the effect sizes for FPS and HR were in the same direction in the general hospital dissociation sample compared to PTSD-unknown dissociation sample, in which all of the comparison groups are of similar race, we feel that the findings are unlikely due primarily to racial differences.

Overall, our findings support the notion that individuals with PTSD and dissociation exhibit a hypoactive sympathetic, and hyperactive parasympathetic response during fear conditioning. Results from the current study contribute to literature suggesting that those with dissociative symptoms represent a distinct subtype of individuals with PTSD, and they extend prior research by identifying convergent externally valid indicators of dissociation (i.e., dampened startle response). Future research is needed to better understand underlying

neural mechanisms that contribute to differential fear conditioning responses and how they affect treatment response. This is especially important given the known role of fear conditioning in the development and maintenance of PTSD, as well as its related role in empirically supported treatments.

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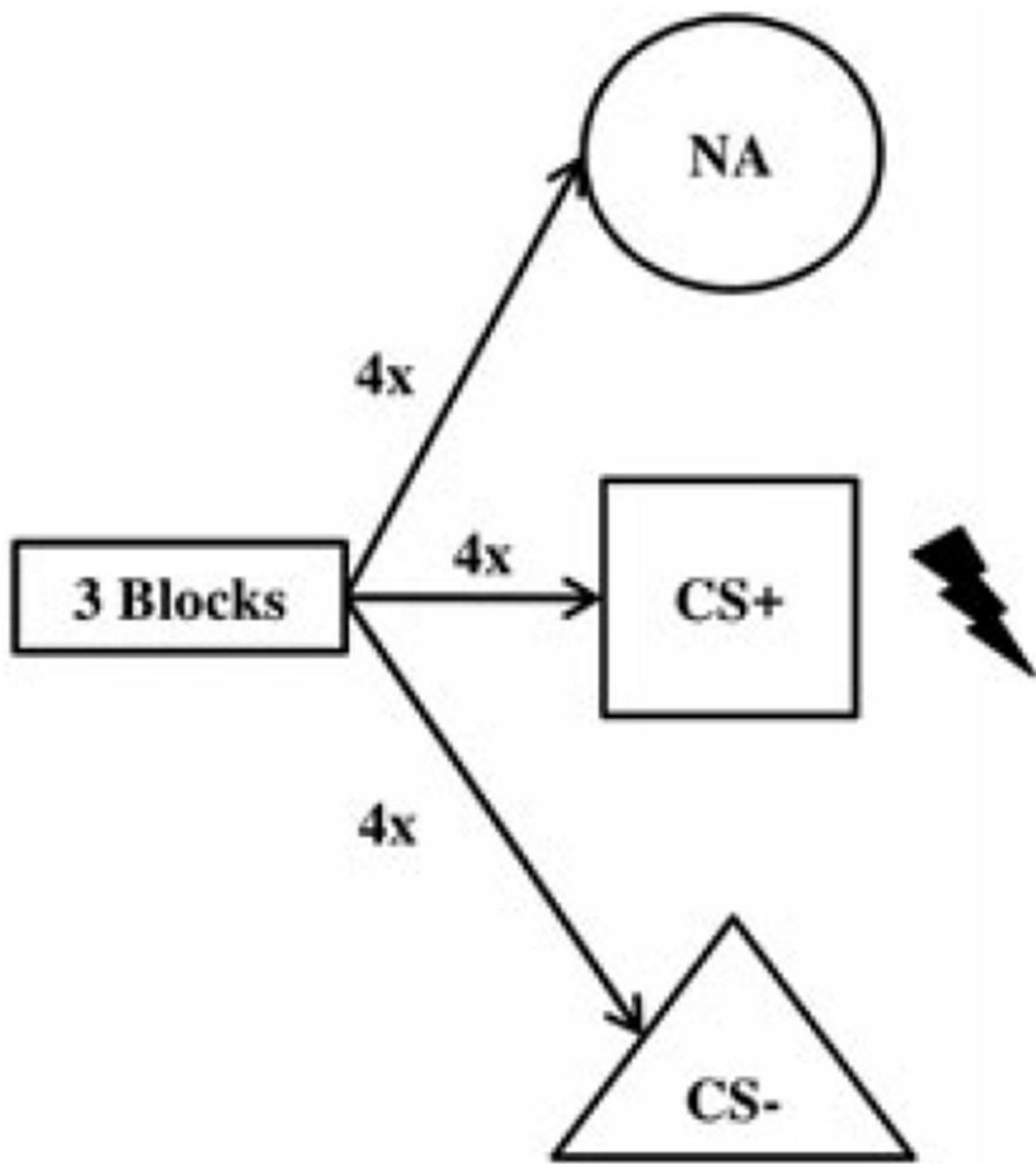
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**FIGURE 1.**

Overview of stimuli presentations in the FPS acquisition phase. CS+: conditioned stimulus paired with airblast; CS-: conditioned stimulus not paired with airblast; FPS: fear-potentiated startle; NA: noise-alone

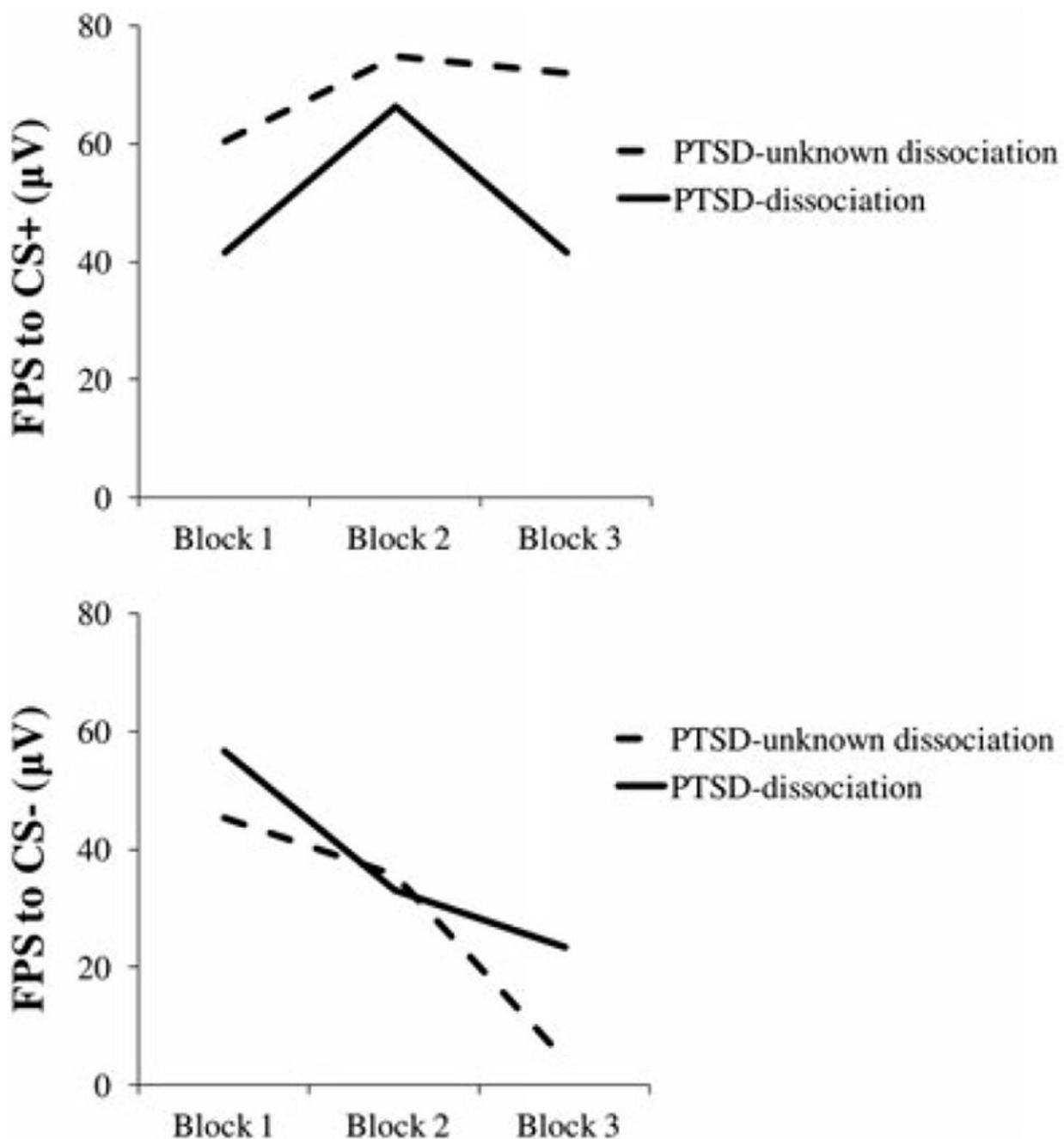


FIGURE 2.
FPS to the CS+ and CS- across all blocks in PTSD-unknown dissociation versus PTSD-dissociation. CS+: conditioned stimulus paired with unconditioned stimulus; FPS: fear-potentiated startle; PTSD: posttraumatic stress disorder

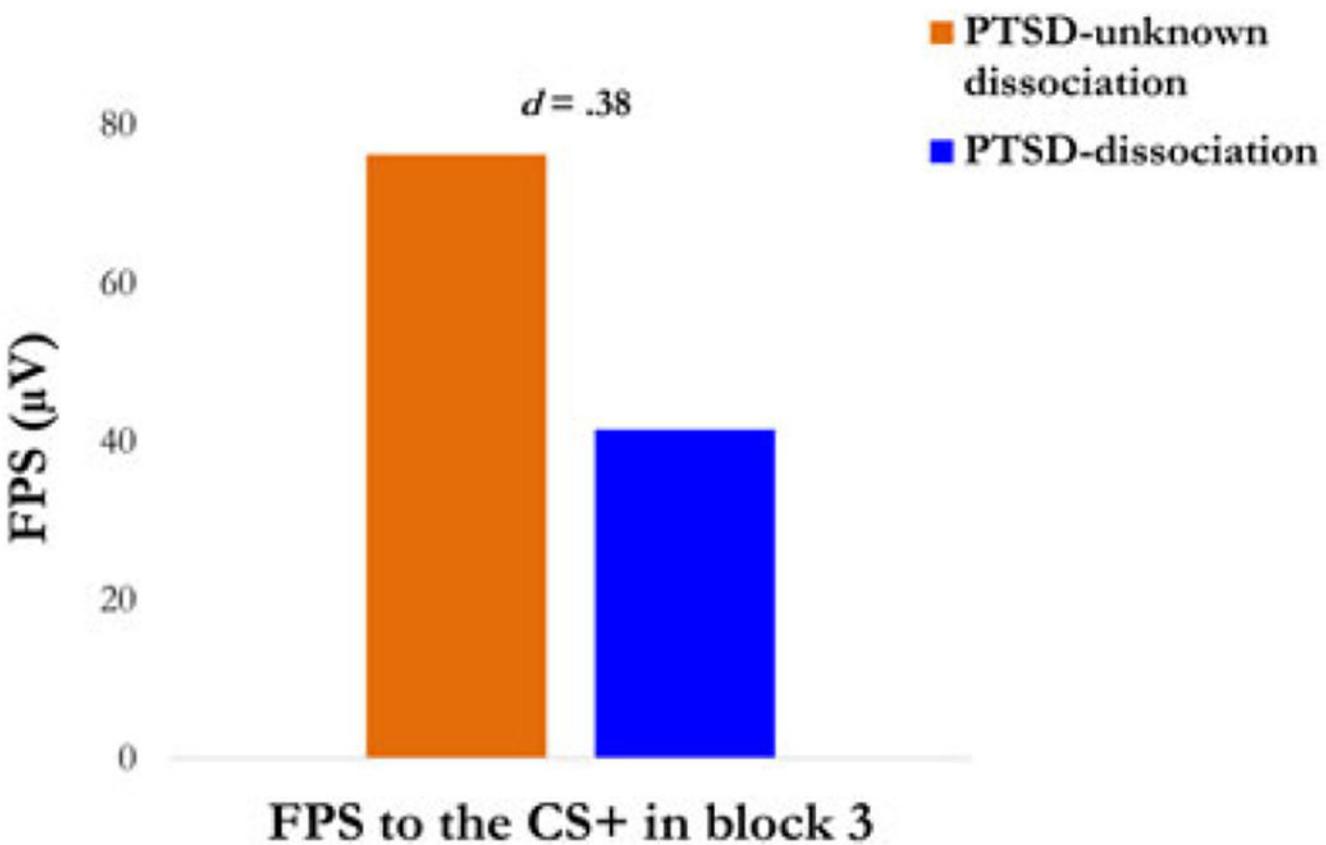
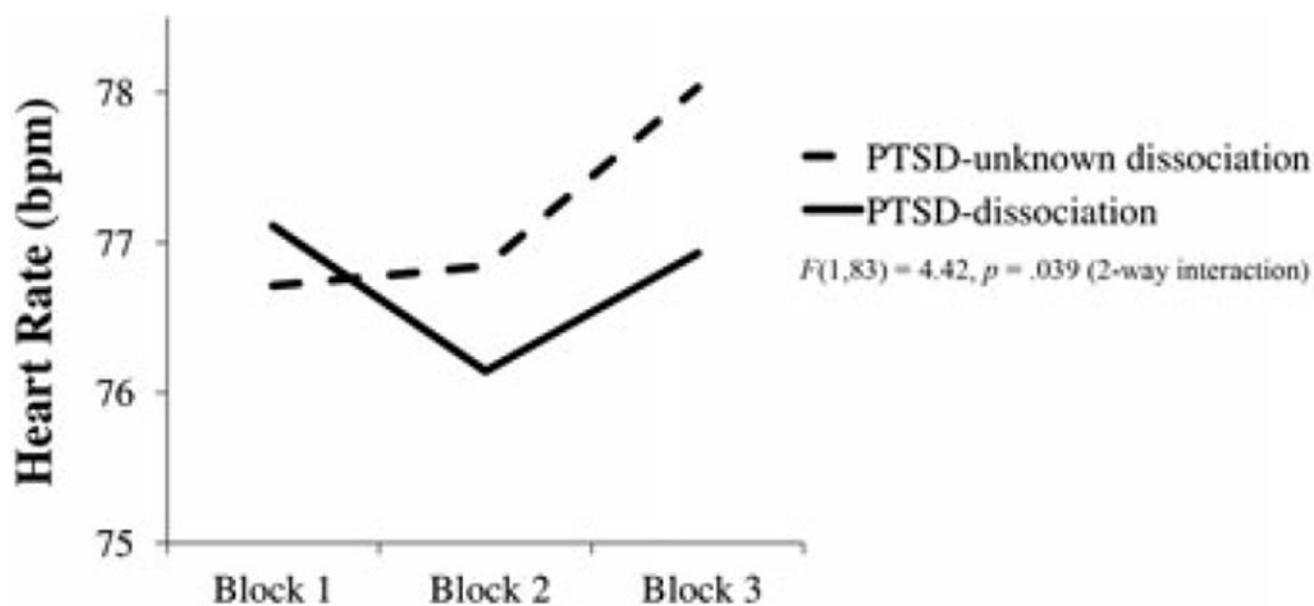


FIGURE 3.

FPS to the CS+ during Block 3 in PTSD-unknown dissociation versus PTSD-dissociation. CS+: conditioned stimulus paired with unconditioned stimulus; FPS: fear-potentiated startle; PTSD: posttraumatic stress disorder

**FIGURE 4.**

Heart rate across all blocks in PTSD-unknown dissociation versus PTSD-dissociation. bpm: beats per minute; PTSD: posttraumatic stress disorder

Participant demographic and childhood trauma data

TABLE 1

Demographics	PTSD-unknown dissociation (n = 53)	PTSD-dissociation (n = 39)	Group difference
Race (% African American)	96.23	42.86	
Current age (M)	38.79	38.74	$t(1,92) = -0.42, p = 0.675$
Education (% with some college)	24.53	26.19	
Childhood Trauma	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	
CTQ Emotional Abuse	13.16 (5.80)	14.98 (6.84)	$t(1,91) = 1.36, p = 0.178$
CTQ Physical abuse	10.90 (5.87)	10.93 (5.56)	$t(1,91) = 0.02, p = 0.985$
CTQ Sexual abuse	12.96 (7.38)	14.80 (7.64)	$t(1,91) = 1.17, p = 0.244$
CTQ Emotional neglect	11.67 (5.86)	14.02 (6.08)	$t(1,91) = 1.89, p = 0.063$
CTQ Physical neglect	8.03 (4.25)	8.98 (4.12)	$t(1,91) = 1.09, p = 0.281$

Note. CTQ: Childhood Trauma Questionnaire; PTSD: posttraumatic stress disorder; *SD*: standard deviation.

Bivariate correlations among MID subscales and FPS, SCR, and RSA ($n = 20$; psychiatric sample)

	1	2	3	4	5	6	7	8	9	10	11
1. MID mean	-										
2. MID depersonalization	0.90 ***	-									
3. MID derealization	0.76 ***	0.84 ***	-								
4. MID depersonalization/derealization mean	0.86 ***	0.96 ***	0.97 ***	-							
5. MID partially dissociated intrusions	0.96 ***	0.82 ***	0.66 ***	0.77 ***	-						
6. FPS to CS+ late acquisition	-0.25	-0.17	0.07	-0.05	-0.27	-					
7. FPS to CS- late acquisition	-0.18	-0.20	-0.09	-0.15	0.01	0.17	-				
8. SCR to CS+ late acquisition	0.20	0.02	0.08	0.05	0.28	-0.17	0.35 ***	-			
9. SCR to CS- late acquisition	0.38 ***	0.40 ***	0.23	0.32 ***	0.35 ***	-0.17	-0.13	0.03	-		
10. HR acquisition change	-0.18	-0.08	-0.14	-0.12	-0.28	0.29	-0.19	-0.31 ***	-0.23	-	
11. RSA acquisition change	0.20	0.25	0.39 ***	0.33 ***	0.16	0.09	0.02	-0.19	0.14	-0.29	-
Mean	40.51	44.67	36.16	40.42	43.05	46.80	20.61	-0.01	0.06	-1.16	-0.18
SD	20.22	21.40	24.19	21.88	24.01	67.63	48.38	0.14	0.16	4.55	1.77
Minimum	8.30	2.50	0.00	1.25	6.45	-30.58	-110.57	-0.23	-0.12	-11.40	-5.21
Maximum	81.90	86.70	76.70	80.00	83.08	227.44	126.24	0.20	0.50	5.30	5.36

Note. CS: conditioned stimulus; FPS: fear-potentiated startle; HR: heart rate; MID: Multidimensional Inventory of Dissociation; RSA: respiratory sinus arrhythmia; SCR: skin conductance response; SD: standard deviation.

*
 $p < 0.05$.

**
 $p < 0.01$.

\hat{r} effect size medium.

Bivariate correlations among MDI subscales and FPS, SCR, RSA ($n = 19$; general hospital sample)

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. MDI total	-												
2. MDI disengagement	0.86 ^{***}	-											
3. MDI depersonalization	0.59 ^{***}	0.39 ^{***}	-										
4. MDI derealization	0.79 ^{***}	0.72 ^{**}	0.47 [*]	-									
5. MDI emotional constriction	0.82 ^{***}	0.62 ^{***}	0.29	0.59 ^{***}	-								
6. MDI memory disturbance	0.82 ^{***}	0.77 ^{***}	0.33 ^{***}	0.52 [*]	0.57 [*]	-							
7. MDI identity dissociation	0.63 ^{***}	0.35 ^{***}	0.45 ^{***}	0.23	0.43 ^{***}	0.48 [*]	-						
8. FPS to CS+ late acquisition	-0.22	-0.08	-0.14	-0.02	-0.44 ^{**}	-0.14	-0.12	-					
9. FPS to CS- late acquisition	-0.24	-0.23	-0.02	-0.10	-0.44 ^{**}	-0.14	-0.04	0.83 ^{***}	-				
10. SCR to CS+ late acquisition	-0.39 ^{***}	-0.20	-0.03	-0.35 ^{***}	-0.21	-0.45 ^{***}	-0.40 ^{***}	-0.22	-0.41 ^{***}	-			
11. SCR to CS- late acquisition	-0.28	-0.34 ^{***}	0.27	-0.31 ^{***}	-0.28	-0.22	-0.04	-0.39 ^{***}	-0.24	0.40 ^{***}	-		
12. HR acquisition change	-0.13	-0.09	0.11	-0.09	-0.03	-0.30 ^{***}	-0.14	-0.09	-0.22	0.10	0.29	-	
12. RSA acquisition change	0.16	0.24	0.35 ^{***}	0.27	0.04	0.02	-0.08	-0.04	-0.07	0.23	-0.21	-0.29	-
Mean	59.44	11.63	8.86	10.53	11.79	10.16	6.42	49.90	35.83	-0.07	0.07	1.33	-0.05
SD	16.24	3.73	2.38	3.85	4.57	3.40	3.31	96.08	90.60	0.22	0.19	4.78	1.05
Minimum	43.00	7.00	5.00	5.00	5.00	5.00	5.00	-10.32	-73.45	-0.48	-0.14	-7.16	-2.00
Maximum	93.00	21.00	13.00	18.00	22.00	18.00	17.00	321.36	319.40	0.42	0.49	15.87	3.21

Note. CS: conditioned stimulus; FPS: fear-potentiated startle; HR: heart rate; MDI: Multiscale Dissociation Inventory; RSA: respiratory sinus arrhythmia; SCR: skin conductance response; SD: standard deviation.

* $p < 0.05$.

** $p < 0.01$.

[†] effect size medium.