

Fear Extinction in Traumatized Civilians with Posttraumatic Stress Disorder: Relation to Symptom Severity

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Background: The symptoms of posttraumatic stress disorder (PTSD) can be explained, at least in part, as an inability to inhibit learned fear during conditions of safety. Our group has shown that fear inhibition is impaired in both combat and civilian PTSD populations. On the basis of our earlier findings, we employed an established fear extinction paradigm to further explore fear dysregulation in a civilian traumatized population.

Methods: Fear-potentiated startle (FPS) was examined in 127 trauma-exposed individuals with and without PTSD. We used a protocol in which conditioned fear was first acquired through the presentation of one colored shape (reinforced conditioned stimulus, [CS+]) that was paired with an aversive air blast to the larynx (unconditioned stimulus) and a different colored shape that was not paired to the air blast (nonreinforced condition stimulus). Fear was extinguished 10 min later through repeated presentations of the CSs without reinforcement.

Results: Both groups demonstrated successful fear conditioning on the basis of startle and unconditioned stimulus–expectancy ratings; however, participants with PTSD displayed greater FPS responses to the CS+ and nonreinforced conditioned stimulus compared with the group without PTSD. During fear extinction, the PTSD group showed elevated FPS responses to the previously reinforced CS+ during the early and middle stages of extinction. During the acquisition and extinction phases, PTSD participants with higher levels of reexperiencing symptoms exhibited greater potentiated startle responses to the CS+ compared with PTSD participants with lower reexperiencing symptoms.

Conclusions: These results suggest that PTSD is associated with enhanced fear learning and a greater “fear load” to extinguish after conditioned fear is acquired.

Key Words: Anxiety disorders, fear extinction, fear-potentiated startle, psychophysiology, trauma

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric illness with neurobiological abnormalities that can develop after exposure to a life-threatening event. Posttraumatic stress disorder symptoms include persistent reexperiencing of the trauma, avoidance of trauma-related stimuli, and increased arousal (1). These symptoms are believed, in part, to reflect an inability of patients to inhibit conditioned fear, most notably in symptoms of reexperiencing (2–4). From a fear conditioning perspective, the trauma serves as an unconditioned stimulus (US) that elicits an unconditioned response that includes intense fear and arousal. The unconditioned response is then associated with cues or stimuli in the traumatic environment (context) such as sights or smells that become conditioned stimuli (CSs). Through this CS–US association, these cues later produce conditioned responses such as fear and panic despite the absence of the original US. Because of these associations, many reexperiencing symptoms can be characterized as persistent conditioned responses (2,5).

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Posttraumatic stress disorder has been observed in traumatized individuals who have: 1) experienced combat situations such as Operations Iraqi Freedom (6), 2) been victimized by violent crime (7), 3) exposed to a natural disaster such as the 2004 Florida hurricanes (8), or 4) experienced a terrorist attack such as that of September 11, 2001 (9). An effective treatment for PTSD is exposure therapy, a form of extinction learning in which patients are repeatedly exposed to trauma-related stimuli to promote fear inhibition and tolerate the stimuli without suffering extreme fear (10–13).

Our group has examined fear processing in PTSD and its comorbid disorders through the study of the acoustic startle response. This is a well-characterized reflexive response to a sudden acoustic stimulus that is mediated by a simple neural circuit. This reflex is modulated under specific conditions because of Pavlovian conditioning (14). For example, when a subject is presented with a stimulus (e.g., a colored shape, termed the CS) at the same time as an aversive stimulus (e.g., an unpleasant air blast, termed the US), the subject quickly learns that the shape predicts the unpleasant event. Fear-potentiated startle (FPS) is the relative increase in the amplitude of the acoustic startle response when a subject sees a CS that predicts the US. Through the use of FPS methods, our group has shown that both combat (15) and civilian (16) PTSD patients are unable to inhibit fear upon presentation of safety signals.

Previous studies on fear extinction in PTSD patients have suggested that one of the neurobiological mechanisms underlying PTSD symptomatology is impaired inhibition of the amygdala by the prefrontal cortex during extinction learning. For example, Milad *et al.* (17) have reported amygdala hyperactivity during extinction learning and impaired extinction recall or retention, through the use of skin conductance measures, in Vietnam veterans and in a population with diverse trauma histories (18). In addition, an Australian study of civilian trauma victims found a reduction in amygdala activity and an increase in prefrontal

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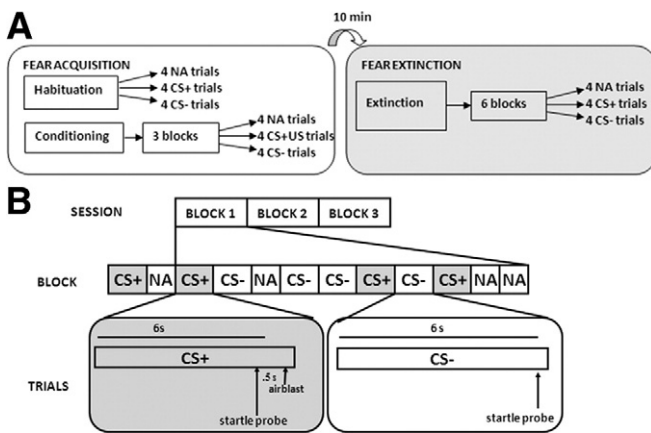


Figure 1. (A) Schematic illustration of the experimental paradigm. (B) Representative breakout diagram of the conditioned stimuli (reinforced conditioned stimulus [CS+] and nonreinforced conditioned stimulus [CS-]) trial types during the Acquisition Session. Note: the previously reinforced CS+ in the Extinction Session did not include the air blast (unconditioned stimulus [US]). NA, noise probe alone.

cortical activity as PTSD symptoms improved with exposure-based treatment (19).

Recent studies from our group and others (20–22) have shown that African Americans with low income living in urban environments represent a high-risk population for experiencing a traumatic event and subsequently developing PTSD. On the basis of these findings and the prior literature, we hypothesized that traumatized individuals with PTSD would display altered fear extinction compared with traumatized individuals without PTSD in an FPS paradigm.

Methods and Materials

Participants

Participants were recruited as part of a larger study investigating the genetic and environmental factors that contribute to PTSD in a primarily African-American, low socioeconomic, inner-city population in Atlanta, Georgia (22,23). Exclusion criteria included active psychosis and major medical illnesses as assessed by history and physical examinations. Participants were also excluded for urine toxicology that was positive for cocaine and hearing impairment. Before their participation, all participants provided written informed consent approved by the Emory University Institutional Review Board.

Psychological Assessment

The following measures were used to index PTSD symptoms, depressive symptoms, childhood trauma history, and adult trauma history, respectively: Modified PTSD Symptom Scale (PSS) (24–26), Beck Depression Inventory (BDI) (27), Childhood Trauma Questionnaire (CTQ) (28,29), and the Traumatic Events Inventory (TEI) (26). These measures have all been used previously in our work with this population (23). The categorical definition of PTSD+ versus PTSD– was determined from responses to the DSM-IV–based PSS questionnaire A–E criteria (A, presence of trauma; B, presence of at least one reexperiencing symptom; C, presence of at least three avoidant/numbing symptoms; D, presence of at least two hyperarousal symptoms; E, occurrence for at least 1 month).

Psychophysiological Assessment

Figure 1A illustrates the experimental session. The FPS protocol consisted of two phases: Fear Acquisition and Fear Extinction. Fear Acquisition began with a habituation phase in which the CSs were

presented without any reinforcement; the conditioning phase consisted of three blocks with four trials of each type (a reinforced conditioned stimulus [CS+]; a nonreinforced conditioned stimulus [CS-]; and the 40-msec, 108-dB noise probe alone [NA]). Figure 1B illustrates the CS trials. Both CSs were colored shapes presented on a computer monitor for 6 sec. The US was a 250-msec, 140-p.s.i air blast directed at the larynx as in our previous studies (16,30). In all phases, the intertrial intervals were randomized to be 9–22 sec.

Ten minutes after Fear Acquisition, participants underwent the Fear Extinction phase. During these 10 min the participants engaged in a trauma-neutral task designed to assess attention. Extinction consisted of six blocks with four trials of each type (the previously reinforced CS+, CS-, and NA) (Figure 1A). None of the CS presentations during Extinction were reinforced with US.

The startle response data were acquired with the electromyography module of the BIOPAC MP150 (Biopac Systems, Aero Camino, California), according to our previously published methods (16). The eyeblink component of the acoustic startle response was measured by electromyography recordings of the right *orbicularis oculi* muscle (15,30,31). The startle probe was a 108-dB(A) sound pressure level, 40-msec burst of broadband noise.

A response keypad (SuperLab, Cedrus Corporation, San Pedro, California) was used during each acoustic startle session to record the expectancy of the participants of the US on each CS presentation (32).

Data Analysis

Demographic and clinical data such as age, PTSD symptoms, and childhood and adult trauma history were compared between the PTSD+ and PTSD– groups with a one-way analysis of variance (ANOVA); categorical data, such as gender and race, were analyzed with χ^2 analyses.

Fear-potentiated startle was calculated with a Difference Score ([startle magnitude in the presence of a CS in each conditioning block] – [startle magnitude to the NA]). These variables were analyzed in a mixed ANOVA with the within-subject factor of Block (three levels for Acquisition; six levels for Extinction), trial type (two levels, CS+ and CS-), and the between-groups factor of Diagnosis (two levels, PTSD+ or PTSD–). Late Acquisition was defined as block 3 of Acquisition, when discrimination learning was at maximum; Extinction was divided into three phases: early (blocks 1 and 2), mid (blocks 3 and 4), and late (blocks 5 and 6) extinction. Significant interactions were followed up by univariate analyses of covariance (ANCOVAs), with depression (BDI), childhood trauma (CTQ), and adult trauma (TEI) used as covariates in all analyses involving diagnostic groups. Baseline startle was measured by comparing average startle magnitude with the NA between diagnostic groups. Contingency awareness was analyzed by comparing US expectancy ratings of each CS trial with a Repeated Measures ANOVA, with diagnostic group as a between-groups factor. All statistical analyses were performed in SPSS 17.0 for Windows (SPSS, Chicago, Illinois), with $\alpha = .05$.

Results

Participants

One hundred twenty-seven participants were enrolled; 78 of which did not meet criteria for PTSD (PTSD–), and 49 who met criteria for PTSD (PTSD+). Table 1 illustrates the demographic and clinical information of the PTSD+ and PTSD– participants.

Clinical Assessment

As shown in Table 1, PTSD+ participants had higher levels of childhood [$F(1,120) = 30.64, p < .001$] and adult trauma [$F(1,126) =$

Table 1. Sample Demographic and Clinical Data

	PTSD (<i>n</i> = 74)	Non-PTSD (<i>n</i> = 123)	
Demographic Data			
Gender (% female)	58.9	55.3	ns
Race (% AA)	95.9	94.3	ns
Age, mean (SD)	41.82 (11.82)	41.64 (13.53)	ns
Trauma History			
Childhood trauma, mean (SD)	51.43 (22.24)	38.97 (15.23)	<i>p</i> < .0001
Z score (CTQ)	.56	-.35	<i>p</i> < .0001
Adult trauma, mean (SD)	4.46 (2.37)	2.76 (2.19)	<i>p</i> < .0001
Z score (TEI)	.41	-.26	<i>p</i> < .0001
PTSD Symptoms			
Total, mean (SD)	25.15 (9.71)	6.66 (6.35)	<i>p</i> < .0001
Reexperiencing, mean (SD)	6.27 (3.81)	1.38 (2.11)	<i>p</i> < .0001
Avoidance, mean (SD)	10.58 (4.39)	2.50 (3.13)	<i>p</i> < .0001
Hyper-arousal, mean (SD)	8.37 (3.65)	2.79 (3.31)	<i>p</i> < .0001

PTSD, posttraumatic stress disorder; CTQ, childhood trauma questionnaire; TEI, traumatic events inventory.

15.26, *p* < .001] than PTSD– participants as determined by the CTQ and TEI, respectively. Note that, although the total trauma levels were slightly higher in the PTSD+ group, the PTSD– group was also a significantly traumatized cohort. Table 1 also presents the trauma levels as standardized Z scores for group comparison.

As expected, PTSD+ participants had higher total PSS scores [$F(1,126) = 203.83, p < .001$] and higher symptom cluster subscores for reexperiencing [$F(1,126) = 89.53, p < .001$], avoidance/numbing [$F(1,126) = 144.80, p < .001$], and hyper-arousal (1,126) = 117.28, *p* < .001] compared with the PTSD– group. The PTSD+ group also reported greater depressive symptoms than the PTSD– group as measured by the BDI [$F(1,125) = 58.09, p < .001$].

Conditioned Fear Acquisition: FPS

There was no Group difference between the PTSD+ and PTSD– groups with regard to baseline (NA) startle response during Fear Acquisition [$F(1,124) = .33, ns$]. During late Acquisition, defined as the third block of the Acquisition phase, participants displayed robust FPS to the CS+ compared with the NA [$F(1,124) = 41.67, p < .001$] with no Group difference between PTSD+ and PTSD– participants (no Block \times Trial Type \times Group interaction and no between-Subjects Effect). In addition, participants demonstrated a significant Block \times Trial Type interaction [$F(2,248) = 8.60, p < .001$] and a clear discrimination between the CS+ and CS–, expressed as a Difference Score, during late Acquisition [$F(1,124) = 15.09, p < .001$], but no significant Block \times Trial Type \times Group interaction.

Figures 2A and 2B show the development of the fear discrimination across blocks for the two groups. There was a significant difference between the PTSD+ and PTSD– groups with regard to startle responses to both trial types as expressed as a Difference Score, during late Acquisition [$F(1,124) = 6.13, p < .05$, see Figure 3A]. The PTSD+ participants displayed greater responding to both the CS+ and CS– compared with the PTSD– group. Note that both groups showed significant discrimination between the CS+ and CS–. The increased response to the CSs in the PTSD+ group remained evident when covarying for depressive symptoms (as measured by BDI score) and adult and childhood trauma exposure [as measured by TEI and CTQ, respectively; $F(1,114) = 5.00, p < .05$]. There was no significant Block \times Trial Type \times Group interaction [$F(1,124) = .90, ns$].

Fear Acquisition Across PTSD Symptom Sub-Clusters

To examine whether the group differences in Acquisition were due to a particular PTSD symptom cluster, we categorized all participants into high- and low-symptom groups, with a median split of the symptoms of each cluster on the PSS, as we have done in our previous work (15,16). With an ANCOVA with BDI, CTQ, and TEI as covariates, we found that individuals who had high reexperiencing symptoms had greater FPS to the CS+ during late Acquisition [$F(1,114) = 8.22, p = .005$] relative to those with low reexperiencing symptoms. High and low avoidance symptom groups did not differ on FPS [$F(1,114) = 2.96, ns$], whereas high and low hyper-arousal groups did [$F(1,114) = 4.39, p < .05$].

Conditioned Fear Acquisition: US Expectancy

Participants rated their expectancy of the US on each CS presentation during Acquisition. During late Acquisition, participants correctly identified the CS+ as predicting the US (DANGER) and the CS– as predicting the absence of the US (SAFETY; $F(1,87) = 198.76, p < .001$) (Figure 3B) with no Group difference between the PTSD+ and PTSD– groups [$F(1,87) = .01, ns$]. There was no significant Block \times Trial Type \times Group interaction and no Between-Subjects Effect [$F(1,87) = 1.26, ns$]. Note that, although the psychophysiological response to fear was markedly increased in PTSD+ subjects, US expectancy was similar between the groups.

Within-Session Fear Extinction: FPS

There was no Group difference between PTSD+ and PTSD– participants with regard to baseline (NA) startle during Fear Extinction [$F(1,116) = .12, ns$] and no difference in startle habituation during Extinction [$F(1,116) = .12, ns$]. Participants displayed significant within-session extinction of FPS to the previously reinforced CS+ [$F(1,114) = 36.35, p < .001$] with a significant Group difference between the PTSD+ and PTSD– groups [Between-Subjects Effect,

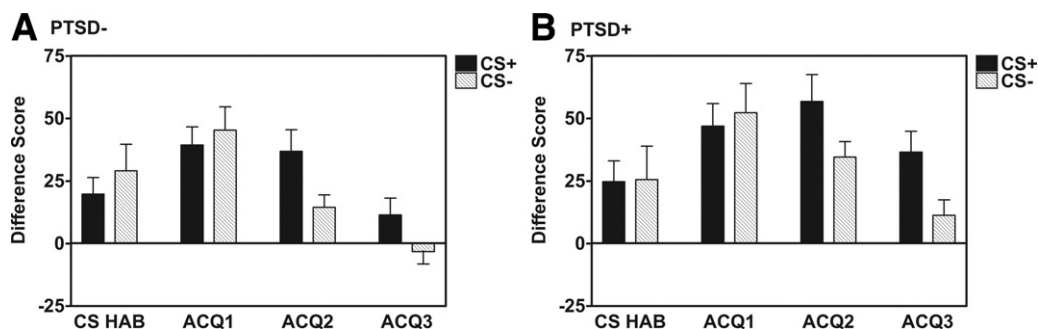


Figure 2. Development of fear-potentiated startle and CS+/CS– discrimination during the Acquisition Session in (A) posttraumatic stress disorder (PTSD)– and (B) PTSD+. Difference score = (mean startle response to the CS+) – (mean startle response to the NA). Significant Block \times trial type interaction ($F(2,248) = 8.60, p < .001$). CS HAB, habituation phase consisting of four presentations each of the NA and the CS+ (without US pairing) and CS–. ACQ, acquisition phase; other abbreviations as in Figure 1.

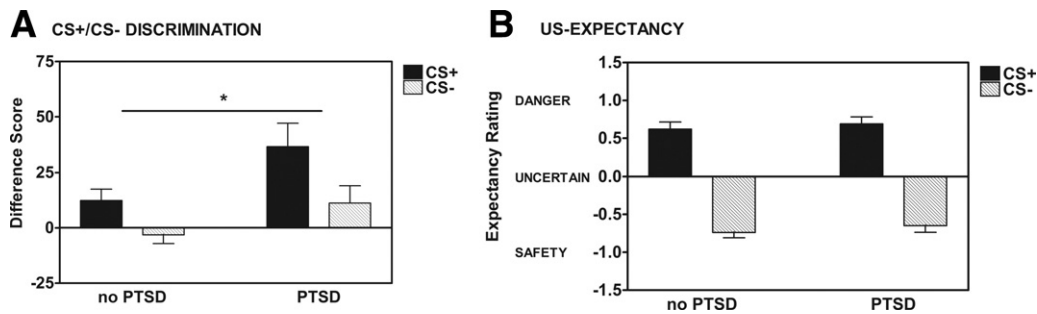


Figure 3. (A) With a fear-potentiated startle paradigm, traumatized individuals with PTSD showed greater potentiated startle responses to the CS+ and the CS–, compared with traumatized individuals without PTSD during late acquisition. Late acquisition was defined as the third block of the fear acquisition phase. Difference score = (mean startle response to the CS) – (mean startle response to the NA). *Analysis of variance, between-subjects effect [$F(1,124) = 6.13, p < .05$]. (B) On the basis of US expectancy ratings, the groups with and without PTSD did not significantly differ in their discrimination between the CS+ and CS– during late acquisition. Responses of DANGER indicated that an individual expected the US on a CS trial and were scored as +1. Responses of UNCERTAIN were scored as 0, and responses of SAFETY indicated that an individual did not expect the US on a CS trial and were scored as –1. Abbreviations as in Figures 1 and 2.

$F(1,114) = 4.06, p < .05$, but no significant Block \times Group interaction, $F(1,114) = 1.00$, ns] (Figure 4A). The PTSD+ group exhibited a greater degree of FPS to the previously reinforced CS+ during Extinction compared with the PTSD– group, an effect that remained evident when covarying for depressive symptoms and adult and childhood trauma [$F(1,104) = 10.03, p < .01$]. When covarying for depressive symptoms and trauma history, there was a significant Block \times Group interaction [$F(1,104) = 3.97, p < .05$]. We found that the PTSD+ subjects had higher FPS during early (first two blocks) and mid (blocks 3 and 4) Extinction than the PTSD– subjects. By late Extinction (blocks 5 and 6), both groups had low fear potentiation to the extinguished CS+.

During Extinction, there were no group differences in startle to the CS– [$F(1,113) = .20$, ns], no significant Block \times Trial Type \times Group interaction, and no significant Between-Subjects Effect [$F(1,113) = 1.65$, ns].

Within-Session Fear Extinction: US Expectancy

As in Acquisition, participants rated their expectancy of the air blast US on each CS presentation. The PTSD+ and PTSD– groups exhibited a significant reduction in ratings of DANGER on CS+ trials [$F(1,47) = 16.30, p < .001$] (Figure 4B) with no Group difference between PTSD+ and PTSD– groups [Trial \times Group interaction,

$F(1,47) = 1.03$, ns; Between-Subjects Effect, $F(1,47) = .48$, ns]. Note that—as with the US expectancy in the preceding text—in contrast to the different physiological levels of expression of fear, both the PTSD+ and PTSD– groups demonstrated equivalent US expectancy across Extinction.

Fear Extinction Across PTSD Symptom Sub-Clusters

To examine whether the group differences in Extinction were due to a particular PTSD symptom cluster, we categorized all participants into high- and low-symptom groups, with a median split of the symptoms of each cluster on the PSS. With an ANCOVA including BDI, CTQ, and TEI as covariates, we found that individuals with high reexperiencing symptoms had greater fear potentiation during early Extinction [$F(1,104) = 5.67, p = .02$] and midextinction [$F(1,104) = 5.96, p = .02$] relative to low reexperiencing participants (Figure 5). The two groups with different levels of reexperiencing symptom severity had equivalently low levels of fear in late Extinction [$F(1,104) = .07$, ns], as with the PTSD group differences. The high- and low-symptom groups for avoidance [$F(1,104) = 2.93$, ns] and hyper-arousal [$F(1,104) = 1.35$, ns] symptoms did not differ in any phase of Extinction.

To determine whether fear inhibition deficits contributed to the extinction effects observed in the PTSD+ group, we explored the

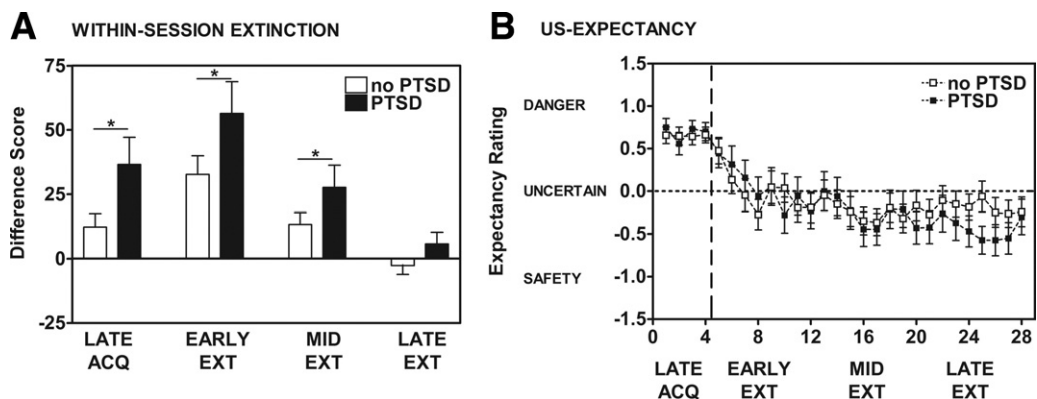


Figure 4. (A) During Early and Mid-Extinction, individuals with PTSD (dark bars) displayed higher fear-potentiated startle responses to the previously reinforced CS+ compared with those without PTSD (open bars). *Analysis of variance, significant between-subjects effect [$F(1,114) = 4.06, p < .05$]. (B) On the basis of US expectancy ratings, the groups with and without PTSD did not significantly differ in their expectancy of the US during the fear extinction phase. Both groups exhibited a reduction in their expectancy of the US as the fear extinction phase progressed [$F(1,47) = 16.30, p < .001$]. Responses of DANGER indicated that an individual expected the US on a CS trial and were scored as +1. Responses of UNCERTAIN were scored as 0, and responses of SAFETY indicated that an individual did not expect the US on a CS trial and were scored as –1. Abbreviations as in Figures 1 and 2.

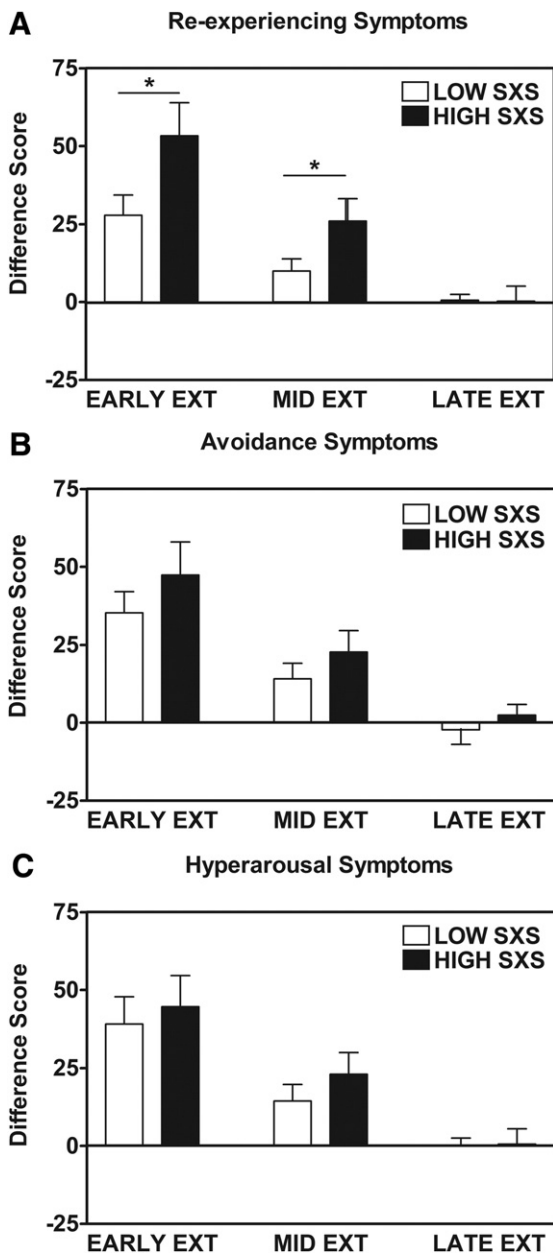


Figure 5. A median split was performed on the basis of the PTSD symptom cluster scores on the PTSD symptom scale. **(A)** Reexperiencing symptoms; **(B)** avoidance symptoms; **(C)** hyperarousal symptoms. When comparing individuals with higher reexperiencing symptoms (SXS) with those with lower reexperiencing symptoms, potentiated startle responses to the reinforced CS+ were greater in the high SXS group. *Analysis of variance with Beck Depression Index, Childhood Trauma Questionnaire, and Traumatic Event Inventory scores as covariates [Early extinction: $F(1,109) = 5.67, p = .019$, and Mid-Extinction: $F(1,109) = 5.96, p = .016$]. Early, mid-, and late extinction were defined as the mean difference scores to the CS+ for the first, middle, and last two blocks of the six blocks of extinction. Other abbreviations as in Figures 1 and 2.

relationship between FPS to the CS– during Acquisition and within-session Extinction with the previously reinforced CS+ during the latter phase. We categorized the PTSD+ participants into high and low responders to the CS– during late Acquisition with a median split of FPS response to the CS– in the third block of Acquisition. High responders were categorized as “poor inhibitors,” and low

Table 2. Hierarchical Regression Analysis

Predictors	Dependent Variable					
	Early Extinction FPS			Late Extinction FPS		
	ΔR^2	ΔF	p	ΔR^2	ΔF	p
Depression	.07	3.05	.09	.01	.38	.54
Trauma history	.03	.53	.59	.02	.32	.73
FPS to danger cue	.46	36.48	.001 ^a	.003	.12	.72
FPS to safety cue	.04	3.29	.08	.22	9.89	.003 ^b

FPS, fear-potentiated startle.

^a $p \leq .001$.

^b $p \leq .01$.

responders were categorized as “good inhibitors.” We then examined within-session extinction in good and poor inhibitors to the previously reinforced CS+ as a means of assessing their ability to inhibit fear to the newly “safe” CS. We found that poor inhibitors did not show a significant decrease in FPS during early, mid, or late Extinction, covarying for levels of adult and childhood trauma and depressive symptoms, [$F(1,16) = 1.28, ns$]. Conversely, the PTSD+ subjects who showed a decreased response to CS– during late Acquisition (i.e., good inhibitors) had a significant decrease in potentiated startle responses to the previously reinforced CS+ during Extinction [$F(1,16) = 21.37, p < .001$].

To assess whether high fear expression and low fear inhibition during late Acquisition independently accounted for deficits in extinction in PTSD+ subjects, we performed hierarchical stepwise regression analyses entering depression in the first step, trauma history in the second step, FPS to the CS+ (DANGER cue) during late Acquisition, and FPS to the CS– (SAFETY cue) during late Acquisition in the final step. We performed separate regression analyses with early and late Extinction entered as a dependent variable (Table 2). Although the overall model with all four predictors was significant [$F(5,39) = 10.14, p < .001$] and accounted for 54% of the variance in early Extinction, neither depression nor trauma history had significant contributions. However, fear potentiation to the CS+ during late Acquisition accounted for 46% of the variance in early Extinction beyond depression and trauma history [$F_{\text{change}}(1,35) = 36.49, p < .001$]. Fear potentiation to the CS– was not associated with early Extinction. By contrast, the hierarchical regression analyses with late Extinction as the dependent variable and the same predictors as in the preceding text entered as independent steps revealed the opposite association. Potentiated startle in late Extinction was not associated with high fear expression to the danger cue but rather to high fear potentiation to the safety cue, which alone accounted for 22% of the variance [$F_{\text{change}}(1,34) = 9.89, p = .003$].

Discussion

An inability to inhibit learned fear under conditions of safety can underlie several PTSD symptoms, most notably reexperiencing (3,5). Our group has previously shown fear inhibition deficits in response to safety cues in both civilian (16) and combat PTSD patients (15). In the present study, we expanded this investigation of fear inhibition in PTSD with an FPS extinction paradigm employed in our prior investigations (30,31). The primary findings of the current study are: 1) both PTSD+ participants and traumatized PTSD– individuals displayed robust FPS to the CS+ and significant discrimination between the CS+ and CS– during Acquisition; 2) the PTSD+ group showed increased FPS to both the CS+ and CS– compared with the PTSD– group during late Acquisition; 3) indi-

viduals with higher reexperiencing and hyper-arousal symptoms—as measured by the PSS—showed greater levels of fear to the CS+ and CS– during Acquisition, compared with those with lower reexperiencing and hyper-arousal symptoms; 4) the PTSD+ group showed increased FPS to the previously reinforced CS+ compared with the PTSD– group during early and middle Extinction; 5) individuals with higher reexperiencing symptoms showed increased FPS to the previously reinforced CS+ compared with the low reexperiencing group during Extinction; 6) elevated FPS responses to the CS– (safety) during Acquisition predicted greater FPS to the previously reinforced CS+ during Extinction; and 7) within the PTSD+ group, those who were poor inhibitors to the CS– demonstrated delayed extinction of fear. This final finding suggests that there might be two separate subgroups within the PTSD cohort, one with a primary phenotype of enhanced fear expression, and a second with impaired inhibition of fear and delayed extinction.

With FPS, we have shown alterations in fear processing in both combat-related PTSD (15) and civilian PTSD (16). In our previous studies using a conditional discrimination paradigm, we have consistently found that PTSD is associated with impaired inhibition of fear (15,16) and a lack of CS+/CS– discrimination when more ambiguous cues are used (16). The present study used a simple discrimination task that reduces the level of ambiguity involved in learning. The result of this simplified task was heightened fear expression to the CS+, which was more than twofold greater in the PTSD subjects compared with the traumatized control subjects during late Acquisition. This exaggerated fear expression was also observed in early and mid Extinction, so that fear potentiation to the CS+ continued to be high in the PTSD group after the CS+ was no longer reinforced. Although the sample in the present study was not medication free, the use of psychotropic medication was low and equally distributed across groups; therefore, medication effects did not account for the observed group differences.

Although most fear conditioning studies in PTSD, including our own, have found deficits in safety cue processing (i.e., diagnostic group differences were greater in responses to CS– than group differences to the CS+) (16,33), neuroimaging data showing amygdala hyper-activation in response to fear-related cues in PTSD would support the finding of heightened fear expression (34,35). To selectively account for responses to danger and safety cues, we then selected PTSD individuals who were also high responders to the CS– during late Acquisition, when CS– potentiation should be low. These individuals, who seemed to be poor inhibitors of fear when learning the safety cue, were also impaired in Extinction. In addition, they did not show decreased startle potentiation to the CS+ in the extinction phase. Given that extinction is thought to be a new inhibitory learning rather than erasure of the original fear memory (36), similar neural mechanisms might be involved in safety signal processing and extinction of responses to danger signals.

It is important to note that heightened fear expression resulted in an impairment at the onset of extinction, in that PTSD subjects exhibited significantly more fear during early and mid Extinction relative to control subjects; however, it did not eliminate extinction altogether—there were no group differences in late Extinction. Therefore, given enough trials, exaggerated fear might be overcome. By contrast, PTSD participants who showed a deficit in safety cue processing did not show extinction even after six blocks. Therefore, it is possible the heightened fear expression accounts for deficits in extinction rate, whereas impaired fear inhibition accounts for an inability to extinguish danger cues. The observed elevation in FPS to the previously reinforced CS+ during the early and middle stages of the fear extinction session has clinical impli-

cations for the treatment of PTSD. Fear extinction is an analogue of clinical interventions such as prolonged exposure therapy (4) that rely on the repeated presentation of trauma-related stimuli (CSs) under conditions of safety (i.e., devoid of noxious consequences). Recent translational work has suggested that d-cycloserine or other novel cognitive enhancers might facilitate exposure-based psychotherapy and reduce the number of exposure sessions required to reduce fear (37–40). The present results suggest the use of this paradigm as a model for the preclinical assessment of novel extinction facilitators as treatment options for PTSD, especially for those participants in which reexperiencing symptoms produce the greatest degree of impairment.

Notably, the current study sample consisted predominantly of African-American participants, which might potentially reduce generalizability to other populations. To our knowledge, there have been no reports of ethnic/racial differences in the acquisition and extinction of FPS. We have, however, reported differences in baseline startle levels between European Americans and African Americans (41). In most of our previous studies (which included Caucasian and African-American participants) individuals who displayed low baseline startle responses consistently showed a robust increase in startle upon introduction of the conditioning paradigm.

An intriguing question raised is the degree to which the PTSD+ and PTSD– participants would recall extinction learning when tested after an elapsed period. Prior research has shown that extinction recall is impaired in PTSD (17,18). The sensitivity in detecting extinction recall deficits with paradigms such as this remains unclear, given that there are conflicting results. For example, we have previously observed spontaneous recovery in psychiatrically healthy volunteers with the same paradigm as that administered in the current study (30), whereas other groups (e.g., Milad *et al.* [18]) have not reported this effect; however, the latter group employed skin conductance and not FPS. Extinction recall studies are underway in the urban traumatized population described herein.

These results suggest that extinction deficits might be due to two independent mechanisms: high fear load might account for exaggerated fear at the onset of extinction, whereas low fear inhibition might account for deficits in fully extinguishing fear responses. In relation to PTSD symptoms, these two mechanisms might be related to differential symptom presentation, so that higher fear load might be associated with reexperiencing, whereas lower fear inhibition might be associated with hyper-arousal (16). Furthermore, it is possible that these two mechanisms have different albeit interconnected neural underpinnings. High fear load and reexperiencing might be associated with hyperactivity in the amygdala (42), whereas impaired fear inhibition—both during fear conditioning and extinction—might reflect altered prefrontal control of the amygdala (43). Although the reexperiencing symptoms seem to be most strongly related to fear load, the high correlation between symptom sub-clusters and total PTSD symptoms makes it difficult to parse out the unique contribution of reexperiencing versus overall symptom severity.

The current findings suggest that PTSD participants experience a greater “fear load” after the acquisition of conditioned fear and that this elevated level of fear might persist after acquisition. The observed increase in FPS to the CS+ after acquisition and during extinction is consistent with previous neurobiological data showing amygdalar hyperactivity and prefrontal cortical hypoactivity in PTSD. In addition, elevated fear levels in PTSD participants are most pronounced during early stages of extinction, suggesting that enhancement of extinction learning (e.g., via pharmacological interventions such as d-cycloserine) might prove beneficial in treating PTSD. The extinction paradigm employed here, which demonstrates robust effect sizes supporting

smaller study designs, might serve as an effective psychophysiological tool for assessing preclinical candidate drug efficacy as well as an objective measure of clinical outcome in PTSD treatment groups with extinction-based exposure therapies.

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