Adversity in early and mid-adolescence is associated with elevated startle responses to safety cues in late adolescence

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Abstract:

Elevated responding to safety cues in the context of threat is associated with anxiety disorder onset, but pathways underlying such responding remain unclear. In this study, we examined whether childhood/adolescent adversity was associated with larger startle reflexes during safe phases of a fear-potentiation startle paradigm (following delivery of an aversive stimulus) that predict anxiety disorders. Participants (N = 104) came from the Youth Emotion Project, a longitudinal study of risk factors for emotional disorders. Participants with no baseline psychopathology underwent a startle-modulation protocol and assessment for childhood and adolescent adversities using a validated interview. Adolescent adversity was associated with larger startle reflexes during the safe phases following an aversive stimulus. Neither child adversities nor adolescent adversities were associated with responding during any other phase of the protocol. These findings suggest a pathway between adolescent adversity and a risk factor for anxiety disorders in which adolescent adversity contributes to impaired responding to safety cues.

Keywords: startle | safety signals | childhood adversity | anxiety disorders

Article:

Several studies have suggested that individuals with anxiety disorders show a failure to inhibit fear responding to cues that signal safety in a context of threat. For example, such individuals typically show elevated eye-blink startle responses (SRs) to a conditional stimulus not paired with an unconditional aversive stimulus (i.e., CS–) within differential conditioning paradigms (for reviews, see Craske, Rauch, et al., 2009; Lissek et al., 2005). In addition, individuals with anxiety disorders show elevated responses throughout extinction and at extinction recall to cues that used to signal the aversive stimulus but now signal safety. More direct evidence for deficits in safety

learning comes from conditional discrimination paradigms (AX+/BX–; Jovanovic, Norrholm et al., 2009), in which individuals with anxiety (posttraumatic stress disorder, PTSD) show deficits in the acquisition and transfer of safety. In other words, when the danger cue (A, which was previously paired with the unconditional stimulus) and safety signal (B, which was previously paired with no unconditional stimulus) are paired (AB), B does not inhibit responding to A in individuals with PTSD to the same extent as in individuals without PTSD (i.e., individuals with PTSD show slower fear extinction).

In our earlier work, we established that elevated fear responding to a conditional stimulus paired with an unconditional stimulus (CS+) and a CS– during extinction and at extinction recall was characteristic not only of youths with anxiety disorders but also of youths at risk for anxiety disorders (Craske et al., 2008).1 In addition, in a related fear-potentiated startle protocol, we found that larger responses to safe phases within a series of alternating danger (i.e., potential for shock) and safe (i.e., no potential for shock) phases were associated with high levels of neuroticism (Craske, Waters, et al., 2009), which is a risk factor for anxiety disorders (e.g., Krueger, Caspi, Moffitt, Silva, & McGee, 1996). Furthermore, overresponding to safe phases was a prospective predictor of the onset of anxiety disorders during 3 years of follow-up (Craske et al., 2011). These studies suggest that failure to attenuate fear responding to safe cues in a context of threat is a risk factor for anxiety disorders.

Elevated fear responding to safe cues may serve to enhance the generalization and persistence of fear responding following discrete negative life events and thereby contribute to excessive and persistent anxiety. As an example, a child who is bullied on the playground and is prone to anxiety may then show excessive fear of other friendly children on the playground. Other than neuroticism (Craske, Waters, et al., 2009), additional factors that underlie elevated fear responding to safe cues have not yet been studied. Given that elevated responding during safe phases is a risk factor for anxiety disorders (Craske et al., 2011), understanding contributory factors to elevated fear responding to safety may help to define the pathways through which anxiety disorders develop.

One possibility is that early life adversities result in elevated fear responding to safe cues, which in turn then increases risk for anxiety disorders. Indeed, various types of childhood adversity have been associated with several anxiety disorders (e.g., Kilpatrick et al., 2003), including physical abuse (e.g., MacMillan et al., 2001), emotional abuse and neglect (Gibb, Chelminski, & Zimmerman, 2007; Lochner et al., 2002), and sexual abuse (Cougle, Timpano, Sachs-Erricson, Keough, & Riccardi, 2010; Kendler et al., 2000). However, the mechanisms contributing to the development of these associations are not well understood. It is conceivable that early adversity may be associated with increased risk of anxiety disorders because adversity elevates fear responding to safety in the context of threat. The viability of this model rests on first demonstrating an association between childhood adversity and elevated fear responding to safety.

A small body of research has shown an association between childhood trauma and larger eye-blink reflexes to startling sounds (Jovanovic, Blanding, et al., 2009; Pole et al., 2007). However, in only a few studies have researchers examined the link between early adversity and responding to safety versus threat, and results from those studies did not indicate the expected link specifically between adversity and elevated responding during safe phases following an aversive stimulus. Instead, findings have been mixed. For example, an animal study indicated that early life adversity is associated with elevated startle reflexes across all phases of a fear-conditioning paradigm (with the finding driven by startle during threat signals, or the CS+; Nelson et al., 2009). Furthermore, in human studies, researchers have observed larger startle reflexes in a child abuse

group compared to a no–child abuse group during only the baseline phase of a conditional discrimination paradigm in one study (Jovanovic, Blanding, et al., 2009) and during the safe as well as the danger phases of a fear-potentiated startle paradigm in another study (Pole et al., 2007).2

Taken together, these studies have demonstrated that early adversity is associated with elevated fear responding in general or to threat cues but not specifically to safe cues. However, these studies are limited in ways that may have mitigated their ability to detect the effects of life adversity on fear responding specifically to safe cues. First, researchers in some of the studies either did not take into account anxiety symptoms that may have been present prior to the fear-conditioning paradigm (Nelson et al., 2009) or included participants with particular anxiety disorders, such as PTSD (Jovanovic, Blanding, et al., 2009). Studies of nondisordered participants who experienced childhood adversity are needed to parse out the effects of the disorder itself. Second, researchers in some of the studies relied on a self-report questionnaire to assess for childhood abuse (Jovanovic, Blanding, et al., 2009; Pole et al., 2007), which has lower reliability than interview measures of childhood abuse (Dohrenwend, 2006; Monroe, 2008).

Third, in only one study (Jovanovic, Blanding, et al., 2009) did researchers assess for different types of child abuse, and in none of the studies did researchers consider the influence of the developmental period during the abuse (i.e., examining the effects of child and adolescent adversities separately). Finally, in none of the studies did researchers examine eye-blink SR in safe and danger phases separately for the phases before and after an aversive stimulus. This distinction may be important given our previous work that has shown that SR specifically during the safe phase following an aversive stimulus predicted anxiety disorder onset (as opposed to safe phases in general or safe phases before the aversive stimulus; Craske et al., 2011).

Because we previously found that elevated startle reflexes during safe phases after delivery of an aversive stimulus were uniquely associated with anxiety disorder onset (Craske et al., 2011), and because of evidence that childhood adversity is associated with anxiety disorder onset (e.g., Cougle et al., 2010), we aimed to examine whether childhood and adolescent adversity are associated with elevated fear responding to safe phases in our fear-potentiation startle protocol. Participants in the current study were part of the Youth Emotion Project (YEP), a longitudinal study examining common and specific risk factors for emotional disorders. Participants with no Axis I psychiatric disorders at baseline underwent a fear-potentiated startle protocol and completed a semistructured interview assessing for the presence and severity of several types of adversity in childhood and adolescence.

Driven by our previous findings, we hypothesized that childhood and adolescent adversity would be associated specifically with elevated startle reflexes during the safe phases that predicted anxiety disorder onset relative to other phases of the startle protocol (i.e., baseline, context, and danger phases) that did not predict anxiety disorder onset. These findings would be consistent with a safety learning–deficit hypothesis. A competing hypothesis, termed generalized defensive responding, derives from the small body of literature that has suggested that those who experienced early life adversity may show elevated responding in general (i.e., baseline startle; Jovanovic, Blanding, et al., 2009) or during threat/danger phases only (Nelson et al., 2009). Thus, we examined child and adolescent adversity in relation to each phase of our fear-potentiation protocol to examine fully the specific associations between child adversity and elevated responding.

Method

Participants

Our data were derived from a larger prospective study, the YEP. Participants were high school juniors recruited during a 3-year period from one school in suburban Los Angeles, California, and another in suburban Chicago, Illinois. Details of the selection procedure, which included oversampling for high neuroticism, are provided elsewhere (Zinbarg et al., 2010). Of the invited participants, 627 completed the baseline assessment, which included the nonpatient edition of the Structured Clinical Interview for DSM–IV (SCID-I/NP; First, Gibbon, Spitzer, & Williams, 2002) and several questionnaires.

Of these participants, 127 completed the startle protocol and the Childhood Trauma Interview (CTI). These 127 participants were part of the larger sample of participants whose data were included in two of our previous articles reporting findings on the startle protocol (Craske et al., 2011; Craske, Waters, et al., 2009) and were part of the larger sample of participants whose data were included in a manuscript reporting findings from the CTI (Vrshek-Schallhorn et al., 2013). The sample was 65.4% female and 34.6% male. Participants self-identified their race/ethnicity as 48.0% Caucasian, 18.9% Latino, 7.1% African American, 5.5% Asian, 5.5% other race/ethnicity, 1.6% Pacific Islander, and 13.4% as having more than one race or ethnicity. At the time of baseline assessment, the sample ranged in age from 15 to 17 years ($M = 16.39$, $SD = 0.51$). At the time the startle protocol was completed, the sample ranged in age from 16 to 18 years ($M = 16.99$, $SD = 0.43$).

The startle-modulation protocol was administered during the first 18 months of the study (1–12 months after the baseline diagnostic assessment). The CTI was administered between 4 and 6 years after the baseline assessment. To examine the effects of childhood and adolescent adversity on startle reactivity without the confound of emotional disorders, we included in the analyses only participants with no current, clinically significant Axis I psychiatric disorder at the baseline assessment; thus, we excluded 23 of the 127 participants.3

Measures

SCID-I/NP Participants were assessed at baseline for Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM–IV; American Psychiatric Association, 1994) psychiatric diagnoses using the SCID-I/NP (First et al., 2002). Interviewers had at least a bachelor's degree and received extensive training and supervision. Each completed SCID-I/NP was presented at a diagnostic consensus meeting led by a doctoral-level supervisor.

CTI The CTI (Fink, Bernstein, Handelsman, Foote, & Lovejoy, 1995) is a semistructured interview that compares positively to similar measures (Roy & Perry, 2004) and that was used here to assess childhood and adolescent adversity retrospectively. Interviews were completed over the phone. Interviewers queried participants about six domains of concrete and behaviorally defined adversity through the age of 16 years, including separations from or loss of a caregiver, caregiver neglect, emotional abuse, physical abuse, witnessing violence, and sexual abuse and assault. For each adversity endorsed, interviewers rated severity, based on more than 260 coding examples in an interview manual, on a scale from 1 (minimal or mild) to 6 (very extreme, sadistic). Thus, the CTI

is designed to elicit reports of a full range of severity of adversities as opposed to only trauma, as the name might suggest.

In previous reports, the CTI had high interrater reliability as well as better convergent and discriminant validity than questionnaires about early life adversity. It also had good predictive validity in its associations with symptoms of dissociation, depression, and PTSD (Brown, Schrag, & Trimble, 2005; Fink et al., 1995; Simeon, Guralnik, Schmeidler, Sirof, & Knutelska, 2001). The CTI's characteristic of eliciting concrete behavioral information rather than judgment or interpretation has been associated with reasonable validity of retrospective reports; positive reports are generally accurate, although underreporting of severe abuse is known to occur with retrospective methods (Hardt & Rutter, 2004).

Because of a significant psychometric flaw in a previously applied scoring system (i.e., multiplying ordinal scales), a novel scoring system was applied in which the sum of adversity severity scores was calculated for each domain of adversity (using CTI data from the YEP; Vrshek-Schallhorn et al., 2013). For example, if a participant experienced three physical abuse events with severity scores of 2, 3, and 4, respectively, the score for physical abuse for that individual would be 9. This scoring system yielded dimensional measures, which tend to provide greater power in comparison to dichotomous measures (e.g., whether a participant did or did not experience a particular type or severity of adversity).

In addition, to permit separate analyses for adversities reported to have occurred relatively early versus later in development, we classified adversities as occurring during early to middle childhood (age 0 to 9 years) or during preadolescence to adolescence (age 9 to 16 years). These ages were chosen because there is evidence of prepubertal gonadal hormone changes beginning at age 9, which might influence sensitivity to adversity (e.g., Romeo, 2010). Within each domain, patterns of adversity were scored separately if they differed in several defining characteristics—perpetrator, duration, frequency, or severity. Taken together, in addition to yielding summed severity scores in both age ranges for each of the six domains of adversity (e.g., witnessing violence in childhood), a total summed score across all six domains was calculated for each age range (i.e., adversities during childhood and adversities during adolescence).

Startle-modulation protocol

The startle protocol included an initial baseline condition, an application of shock electrode condition (i.e., context), and a series of alternating safe and danger phases, during which an aversive electrical biceps muscle contraction was threatened to occur during the final 15 s of danger phases only. Baseline and context conditions were then repeated. Auditory startle stimuli were presented throughout. Contextual modulation was defined as the SR during the electrode application phase. Explicit threat cue modulation was assessed during danger phases relative to safe phases.

Baseline and context conditions For the first baseline condition, eight startle stimuli were delivered with a mean interstimulus interval of 22 s while participants focused on a white fixation cross. The first context condition followed next, during which participants were fitted with two muscle contraction electrodes to the biceps muscle and told that instructions would be given when contractions would happen. Eight startle stimuli were presented while participants focused on the fixation cross.

Fear-potentiation condition Before initiating the safe/danger phases, we told participants that no contractions would be delivered while the words "Safe: no contraction will be given" were on the green screen and that they might receive a contraction when the words "Danger: contraction might be given" were on the red screen. There were eight safe and eight danger phases in alternating order, always commencing with a safe phase. Participants also were told that the progressing bar on each screen would count down from 0 to 55 s and that if a contraction were to occur in the danger phase, it would happen in the last 15 s as the bar turned from pink to red in color. Finally, they were told they might receive a contraction up to three times and of an increasing intensity each time. All participants received only one contraction in the final 15 s of the fourth danger phase. Sixteen startle probes were presented in each phase, with two trials per phase, at 5 and 35 s or at 15 and 45 s, resulting in 32 startle probes during the safe/threat phases.

After the fear-potentiation condition, the muscle contraction electrodes were removed for the second baseline condition. They were reattached for the second context condition. For more methodological detail concerning the startle paradigm, see Craske, Waters, et al. (2009) and Craske et al. (2011), both of which report findings using the YEP sample.

Electrophysiological materials and equipment Auditory startle stimuli (105 dB, zero rise time, 50-ms white noise bursts) were presented binaurally through stereophonic headphones (Sony, Model MDRV700). The amplitude and latency of SRs were measured by electromyogram (EMG) activity of the orbicularis oculi. EMG activity was recorded from electrodes placed beneath the right eye approximately 10 mm apart, edge to edge, and from 9 to 11 mm below the lower lid margin. The lateral electrode was placed 5 mm medial to the outer canthus. A vertical electrooculogram was recorded from electrodes above and below the left eye to facilitate recognition of spontaneous blinks and eye movements. The impedance level of electrodes was 15 kohm or less. EMG activity was amplified by 10,000 with low and high frequency cutoff values of 30 Hz and 1000 Hz, digitized at 1000 Hz, full-wave rectified after analogue-to-digital conversion, and smoothed with a 2-ms moving-average filter.

EMG activity magnitudes were expressed as the difference between the mean amplitude of the 200 ms of EMG activity preceding the startle stimulus and the peak response (between response onset and 104 ms following the startle stimulus). Response onset was defined as the first increment of EMG activity between 20 and 80 ms (response onset window) following startle stimulus onset that exceeded 2 standard deviations above the mean of baseline and did not drop below that level for more than 10 ms. Given the highly skewed nature of startle EMG activity (Yamada, Yamasaki, Nakayama, & Miyata, 1980), analyses were performed on natural log (ln) transformed eye-blink data.

The muscle contraction, delivered by a Digital 807 Electrical Muscle Stimulation Device (Everyway Medical Instruments), was a 20.4-mA peak current (i.e., equating to a 50-V peak) for 0.5 s. The experience of the contraction is one of a very rapid onset, uncomfortable muscle contraction across the biceps for 0.75 s (for more details, see Craske et al., 2011; Craske, Waters, et al., 2009).

Procedure

After signing informed consent, participants completed a baseline diagnostic assessment followed by the startle protocol (1–12 months after study enrollment). The startle protocol was completed by 168 participants, although only a subset of 127 participants completed the CTI as well (n = 74

from Los Angeles and n = 53 from Chicago). The two laboratories used identical hardware, software, manual procedures, and technician training procedures. Participants were seated upright in a sound-attenuated room adjacent to the experimental room, interconnected via intercom and closed-circuit cameras from two angles (Los Angeles) or one-way mirrors (Chicago). Participants were instructed to sit quietly and as still as possible throughout the protocol. From 3 to 6 years (depending on the cohort) after baseline assessment (i.e., in the 6th–7th year of YEP data collection), 127 of the participants who had undergone the startle protocol completed a CTI over the phone.

Statistical analysis

The analyses included 104 participants who completed the startle protocol and the CTI and who did not meet the diagnostic criteria for any DSM–IV–TR (American Psychiatric Association, 2004) Axis I psychiatric disorder at the baseline assessment. A series of hierarchical linear regressions were conducted in SPSS. Each regression examined whether the sum of early life adversity severity scores across all domains for a given developmental period (i.e., childhood or adolescence) predicted SR indices.

Analyses of the safe and danger phase variables included the mean EMG activity SR during the eight trials preceding the safe/danger sequences as a covariate in the first block (i.e., context SR) to account for individual differences in responding before the fear-potentiation portion of the startle protocol. Predictors in the second block included the sum of severity scores across domains of adversity during childhood and adolescence (childhood and adolescent scores were entered in two separate analyses). The dependent variables included (a) safe phase SR before the muscle contraction, (b) safe phase SR after the muscle contraction, (c) danger phase SR before the muscle contraction, and (d) danger phase SR after the muscle contraction. SR for each of these phases was identical to those examined as predictors of anxiety disorder onset in this sample (Craske et al., 2011).

For analyses predicting SR during the safe and danger phases after the administration of the muscle contraction, the SR during those phases before the contraction also were entered into the first block as covariates (e.g., when predicting SR during the safe phase postcontraction, SR during the safe phase precontraction was entered as a covariate). The adjusted R2 is presented as an index of effect size when the adversity predictor variable of interest was entered alone in the model (e.g., childhood adversity predicting SR during baseline pre), and the change in R2 (ΔR2) is reported as an index of the effect size when the adversity predictor variable of interest is added after covarying for other variables (e.g., childhood adversity predicting baseline post, because baseline pre is entered into the first block of the model).

As a secondary analysis, we separately examined child and adolescent adversities as predictors of the two baseline phases (before and after the safe/danger phases) and the two context phases (before and after the safe/danger phases). When predicting the baseline and context phase SR after the safe/danger phases, the respective baseline and context phase SRs prior to the safe/danger phases were entered as covariates. For example, in testing whether childhood adversities predicted responding during the second context phase (that occurred after the safe/danger phases), the SR during the context phase prior to the safe/danger phases was entered in the first block as a covariate.

When child or adolescent adversity was associated with a startle variable, an additional analysis was conducted including all six types of adversity (i.e., separation/loss, neglect, emotional

abuse, witnessing violence, physical abuse, and sexual abuse) entered simultaneously into the model as predictors to examine which, if any, types of adversity were uniquely associated with that startle variable. To be conservative, we ran all analyses a second time, covarying for gender and site to account for variance that may have been explained by these variables. We have reported these findings only when they differed from the main analyses.

Results

Table 1 presents the means and standard deviations for SR in each of the phases of the startle protocol, and Table 2 reports the means and standard deviations for each domain of adversity separated by developmental period.

Table 1. Means (SDs) of SR Magnitudes (Log-Transformed μV) for All Phases

Phase	SR Magnitude
Prebaseline	4.49 (0.79)
Postbaseline	3.53 (1.01)
Precontext	4.25 (0.93)
Postcontext	3.75 (1.00)
Safe pre–muscle contraction	4.06 (0.85)
Safe post–muscle contraction	3.76 (0.93)
Danger pre–muscle contraction	4.29 (0.81)
Danger post–muscle contraction	4.12 (0.85)

Note: SR = startle response.

Table 2. Means (SDs) of Sum of Severity Scores Across Domains of Adversity

	Summed severity score	
Adversity domain	Child	Adolescent
Separation/loss	2.19 (3.40)	2.65 (3.10)
Neglect	1.15 (2.87)	6.11 (4.49)
Emotional abuse	1.87 (1.92)	4.16 (4.03)
Witnessing violence	1.02 (2.29)	1.25 (2.08)
Physical abuse	2.22 (3.14)	1.96 (2.89)
Sexual abuse	0.25 (0.99)	0.26 (1.40)
Across domains	8.69 (9.24)	16.38 (10.83)

Manipulation check

In this subsample, SR was significantly higher in the danger phases compared to the safe phases, $t(206) = -2.71$, $p < .01$. SR did not significantly differ between the baseline and context phases, $t(206) = -0.02$, $p = .98$, or between SR during the fear-potentiation paradigm and the other (baseline and context) phases, $t(206) = 0.44$, $p = .66$. For more details with regard to the larger sample, see Craske et al. (2011).

Analyses of associations between adversity and startle variables

Tables 3 and 4 report the statistics for each of the final models predicting safe and danger phase SR variables with childhood adversity (Table 3) and adolescent adversity (Table 4) as the predictors of interest. Tables 5 and 6 report the statistics for the final models predicting baseline and context phase SR variables with childhood adversity (Table 5) and adolescent adversity (Table 6) as the predictors of interest.

Table 3. Child Adversity Predicting Safe and Danger Phases (Final Models)

Model	*b*	*SE*	β	*t*
Model 1: DV safe precontraction				
Precontext	0.81	.04	0.89	19.92**
Child adversity (sum severity)	−0.004	.004	−0.05	−1.06
Model 2: DV safe postcontraction				
Precontext	0.27	.12	0.27	2.34*
Safe precontraction	0.67	.13	0.61	5.22**
Child adversity (sum severity)	0.01	.01	0.05	1.02
Model 3: DV danger precontraction				
Precontext	0.77	.04	0.88	18.77**
Child adversity (sum severity)	−0.002	.004	−0.02	−0.43
Model 4: DV danger postcontraction				
Precontext	0.23	.10	0.25	2.34*
Danger precontraction	0.67	.11	0.64	5.94**
Child adversity (sum severity)	0.003	.05	0.03	0.67

Note: DV = dependent variable.
*p < .05. **p < .001.

Table 4. Adolescent Adversity Predicting Safe and Danger Phases (Final Models)

Model	*b*	*SE*	β	*t*
Model 1: DV safe precontraction				
Precontext	0.82	.04	0.90	19.94**
Adolescent adversity (sum severity)	0.000	.004	0.001	0.03
Model 2: DV safe postcontraction				
Precontext	0.27	.11	0.27	2.38*
Safe precontraction	0.66	.13	0.60	5.25**
Adolescent adversity (sum severity)	0.01	.004	0.12	2.36*
Model 3: DV danger precontraction				
Precontext	0.77	.04	0.88	18.77**
Adolescent adversity	0.003	.004	0.04	0.78
Model 4: DV danger postcontraction				
Precontext	0.23	.10	0.25	2.31*
Danger precontraction	0.67	.11	0.64	5.95**
Adolescent adversity	−0.003	.004	−0.04	−0.72

Note: DV = dependent variable.
*p < .05. **p < .001.

Table 5. Child Adversity Predicting Baseline and Context Phases (Final Models)

Model	*b*	*SE*	β	*t*
Model 1: DV prebaseline				
Child adversity (sum severity)	−0.01	.01	−0.17	−1.67
Model 2: DV postbaseline				
Prebaseline	1.05	.08	0.81	13.59**
Child adversity (sum severity)	0.004	.04		0.59
Model 3: DV precontext				
Child adversity	−0.01	.01	−0.09	−0.91
Model 4: DV postcontext				
Precontext	0.91	.06	0.85	15.79**
Child adversity	0.000	.01	−0.003	−0.07

Note: DV = dependent variable.
**p < .001.

Table 6. Adolescent Adversity Predicting Baseline and Context Phases (Final Models)

Model	*b*	*SE*	β	*t*
Model 1: DV prebaseline				
Adolescent adversity (sum severity)	0.004	.01	0.06	0.57
Model 2: DV postbaseline				
Prebaseline	1.04	.08	0.81	13.63**
Adolescent adversity (sum severity)	0.004	.05	0.05	0.76
Model 3: DV precontext				
Adolescent adversity	0.01	.01	0.06	0.63
Model 4: DV postcontext				
Precontext	0.91	.06	0.85	15.84**
Adolescent adversity	0.00	.01	0.01	0.09

Note: DV = dependent variable.
**p < .001.

Associations between childhood and adolescent adversity and SR during safe phases To test our safety learning–deficit hypothesis, we first examined whether childhood and adolescent adversities were associated with SR during the safe phases of the startle protocol. The sum of severity scores across domains of childhood adversity was not significantly associated with SR during the safe phases before or after the muscle contraction, ΔR2s = .02 and .03 for safe phases pre– and post–muscle contraction, respectively, ps > .17. The sum of severity scores across domains of adversity during adolescence was not associated with SR during the safe phase before the muscle contraction, ΔR2 = .00, p = .72, but was significantly associated with SR during the safe phase after the muscle contraction, b = 0.01, β = 0.12, t(101) = 2.36, p = .02, adjusted R2 = .74, ΔR2 = .014, F(1, 98) = 5.57, p = .02, such that higher adolescent life adversity severity scores were associated with higher SR during this phase. Consistent with our hypothesis, results showed that adolescent adversity was significantly associated with elevated SR during the safe phase after the aversive stimulus, the variable that predicted anxiety disorder onset in this sample (Craske et al., 2011). However, inconsistent with our hypothesis, results indicated that childhood adversities were not associated with SR during the safe phase after the aversive stimulus.

A series of additional analyses were conducted to examine whether this effect was unique to the safe phase following the muscle contraction and unique to adolescent adversity. First, an analysis was conducted covarying for SR during the danger phases before and after the muscle contraction to examine whether the effect remained significant after accounting for the variance explained by the SR during the danger phases. Adolescent adversity remained significantly associated with SR during the safe phase following the muscle contraction, $b = 0.01$, $\beta = 0.11$, $t(101) = 2.22$, $p = .03$, adjusted $R2 = .75$, $\Delta R2 = .012$, $F(1, 98) = 4.92$, $p = .03$. Second, an analysis was conducted to examine whether the effect was specific to adolescent adversity by covarying for childhood adversity. Adolescent adversity remained significantly associated with the SR during the safe phase following the muscle contraction after accounting for the variance explained by childhood adversity, $b = 0.01$, $\beta = 0.14$, $t(101) = 2.17$, $p = .03$, adjusted $R2 = .74$, $\Delta R2 = .012$, $F(1, 97) = 4.69$, $p = .03$.

Third, we performed an additional analysis covarying for site and gender to account for these individual differences. The effect of adolescent adversity on the safe phase SR following the muscle contraction was similar in magnitude to the previous analyses but did not attain statistical significance, $b = 0.01$, $\beta = 0.13$, $t(101) = 1.94$, $p = .056$, adjusted $R2 = .75$, $\Delta R2 = .01$, $F(1, 95) = 3.74$, $p = .056$. Because the effect was virtually identical in magnitude to the others in this series of analyses, we presumed that the addition of two covariates may have resulted in insufficient power to detect a statistically significant effect. Taken together, these findings indicate that adolescent adversity is uniquely associated with safe phase SR after the delivery of the muscle contraction.

Because adolescent adversity in general was associated with elevated SR during the safe phase following the aversive stimulus, an additional analysis was conducted including all of the domains of adversity entered simultaneously as predictors to examine whether any specific domains uniquely contributed to the model. Only neglect uniquely contributed to the model, $b = 0.03$, $\beta = 0.14$, $t(101) = 2.57$, $p = .012$, adjusted $R2 = .75$; final model including all domains: $\Delta R2 = .03$, $F(6, 93) = 2.11$, $p = .059$, semipartial correlation for neglect = .13, with higher sum of severity scores for the neglect domain associated with higher SR during the safe phase of the startle protocol that followed the muscle contraction. The finding remained significant after accounting for childhood adversity (across domains), $b = 0.01$, $\beta = 0.11$, $t(101) = 2.22$, $p = .03$, adjusted $R2 = .74$; final model including all domains: $\Delta R2 = .03$, $F(6, 92) = 1.91$, $p = .088$, semipartial correlation for neglect = .13. The finding also remained significant after accounting for SR during the threat phases before the muscle contraction, $b = 0.03$, $\beta = 0.13$, $t(101) = 2.57$, $p = .012$, adjusted $R2 = .75$; final model including all domains: $\Delta R2 = .03$, $F(6, 92) = 1.91$, $p = .087$, semipartial correlation for neglect = .13. This finding remained nearly identical when covarying for gender and site, although the effect of neglect only approached statistical significance, $b = 0.02$, $\beta = 0.11$, $t(101) = 1.97$, $p = .052$, adjusted $R2 = .75$, final model including all domains: $\Delta R2 = .03$, $F(6, 91) = 1.80$, $p = .108$, semipartial correlation for neglect = .10. The effect sizes stayed consistent across these analyses, suggesting the analysis covarying for additional individual difference variables (i.e., site and gender) may have resulted in insufficient power to detect a statistically significant difference.

Taken together, these findings suggest that neglect may be partly driving the association between adolescent adversity and deficits in responding to safety cues. It is important to note that neglect accounted for approximately 56% of the variance due to the predictors on this step, indicating that a substantial amount of the variance in safe phase SR following the muscle contraction was accounted for by shared features across the abuse and neglect variables entered on that step (44%).

Associations between childhood and adolescent adversity and SR during danger, baseline, and context phases To test the generalized defensive responding hypothesis, we examined whether childhood and adolescent adversities were associated with the other phases of the startle protocol. The sum of severity scores across domains of childhood adversity was not significantly associated with SR during the danger phases before or after the muscle contraction, $\Delta R2s = .00$ and .001 for danger phases pre– and post–muscle contraction, respectively, $ps > .54$. Similarly, the sum of severity scores across domains of adolescent adversity was not significantly associated with SR during the danger phases before or after the muscle contraction, $\Delta R2s = .001$ for danger phases both pre– and post–muscle contraction, $ps > .40$.

The sum of severity scores across domains of adversity during childhood was associated with the baseline SR neither prior to the fear-potentiation portion of the paradigm nor after the fear-potentiation protocol, adjusted $R2s = .02$ for baseline pre and $\Delta R2 = .001$ for baseline post, $ps > .32$. Nor were childhood adversity scores associated with SR during either of the context phases (prior to or after the fear-potentiation protocol), adjusted $R2s = –.002$ for context pre and $\Delta R2 = .00$ for context post, $ps > .36$. The sum of severity scores across domains of adversity during adolescence was associated with the baseline SR neither prior to the fear-potentiation portion of the paradigm nor after the fear-potentiation protocol, adjusted $R2s = –.01$ for baseline pre and $\Delta R2 = .002$ for baseline post, $ps > .45$. Nor were adolescent adversity scores associated with SR during either of the context phases (prior to or after the fear-potentiation protocol), adjusted $R2s = –.01$ for context pre and $\Delta R2 = .00$ for context post, $ps > .53$. Thus, these data did not support the generalized defensive responding hypothesis that adversities would be associated with elevated SR in general or in phases other than the safe phases.

Discussion

The safety learning–deficit hypothesis was partially supported: Adolescent adversity was significantly associated with larger startle reflexes during safe phases following the aversive stimulus and not during other phases. The results did not extend to childhood adversity. The current study indicates that relatively recent life stressors (i.e., adolescent adversities, which could have occurred up to 2 years before the startle protocol but as long as 8 years before the startle protocol) were associated with elevated responding during safe phases following the aversive stimulus, whereas these data did not yield a significant association with earlier childhood adverse experiences. Furthermore, the effect of adolescent adversity on safe phase startle responding remained statistically significant after accounting for the variance explained by childhood adversity, providing support for the specificity of adolescent adversity as a predictor of SR during the safe phase following the aversive stimulus. It is conceivable that with the passage of time since earlier childhood adversity, and in the absence of subsequent adversity, other protective factors may intervene and buffer the effects of that earlier adversity. Childhood adversity thus might be associated with elevated SR during safe phases if testing was conducted closer to the timing of the adversity (e.g., during early to middle adolescence).

It is important to note that previous studies examining the relationship between childhood trauma and fear-potentiated startle responding (e.g., Jovanovic, Blanding, et al., 2009) or anxiety disorder onset (e.g., Cougle et al., 2010) often used questionnaires and interviews that included adolescent experiences but categorized all adversities occurring before age 18 under the umbrella of childhood trauma or adversity. Thus, it is possible that previous findings were driven by adolescent adversities that were not examined separately. It also is possible that advancing pubertal

status might differentially moderate the relationship between childhood versus adolescent adverse events and subsequent startle reactivity. Indeed, there is some evidence that advancing pubertal status has effects on the psychophysiology of defensive and appetitive responding (Quevedo, Benning, Gunnar, & Dahl, 2009), as well as interactions with increasing stress and emotional symptoms (Conley & Rudolph, 2009; Patton et al., 2008). Another possibility is that low base rates (resulting in data skew) for several childhood adversities (see Table 2) may have resulted in insufficient power to detect effects of childhood adversity on responding to safety cues. Although this is a problem likely to occur in any examination of childhood adversity in a normal, nondisordered sample, it nonetheless should be considered as a viable explanation for the null findings.

It also is important that the prediction of SR was unique to the phase of the paradigm that has been shown to predict anxiety disorder onset (Craske et al., 2011). This finding provides a direction for future research in identifying mediational pathways between the experience of adversity and anxiety disorders. Furthermore, the association between adolescent adversity and SR during the safe phases following the aversive stimulus remained significant after covarying for SR during the danger phases. The competing generalized defensive responding hypothesis—that elevated fear responding in general or to threat cues in particular would relate to early life adversity—was not supported. Thus, the current results were not in accord with previous work examining the associations between startle reflex responses and childhood trauma (i.e., Jovanovic, Blanding, et al., 2009; Nelson et al., 2009; Pole et al., 2007).

More work with consistent methodology across studies is needed to clarify discrepancies in this small body of literature. For example, separating indices of SR before and after an aversive stimulus proved to be an important distinction that was not made in previous work. In the current study, we attempted to improve on previous methodology by (a) using a validated, semistructured interview that assessed for a number of different types of adversities (summed scores represented experiences across six domains of adversity) and a continuous severity rating scale; (b) including only participants without any Axis I psychopathology to avoid potential confounds; and (c) examining two developmental periods separately. The current findings indicate that adverse experiences are specifically associated with elevated fear responding to safe cues following an aversive stimulus. Thus, future research should explore mediational models to examine whether this pattern of elevated responding to safety after an aversive stimulus mediates the association between adolescent adversity and anxiety disorder onset.

The current data indicate that neglect may uniquely contribute to elevated fear responding to safety cues. Conversely, the number of predictors in the model for a sample of this size may have resulted in an underpowered test, particularly for adversity domains that were rarely endorsed, such as sexual abuse, physical abuse, and witnessing violence. Nonetheless, neglect is an understudied area of child and adolescent adversity relative to other types of adversity, such as physical and sexual abuse, and the findings point to the value of further investigation. At present, these data suggest that neglect experiences are associated with elevated fear responding to safety cues that later contribute to anxiety disorders, but why this finding emerged for neglect in particular, above and beyond other types of adversity, is unclear.

It also is worth reiterating that a substantial proportion of the variance in the model including all six domains of adversity was shared across the predictors, suggesting that common features that cut across adversities explain deficits in responding to safety cues. One possible area for exploration is the role of the perpetrator. Specifically, future research might examine whether the familiarity of the perpetrator (e.g., caregiver vs. noncaregiver) moderates these effects. Adverse

events perpetrated by those with whom there is an expectation of safety may be perceived by the child or adolescent as more uncontrollable and more unpredictable, both of which have been theorized to play a role in the development of anxiety and fear (Foa, Zinbarg, & Rothbaum, 1992; Mineka & Kelly, 1989). If impairments in safety responding are most prominent in individuals whose adverse experiences were perpetrated by caregivers, this result would lend support to the idea that violation of safety expectations play an especially significant role in subsequent deficits in responding to safety cues. This theory is consistent with previous work showing that close relationships between the perpetrator and victim are associated more often with PTSD following childhood sexual abuse (e.g., McLeer, Deblinger, Atkins, Foa, & Ralphe, 1988; Ullman, 2007).

The present study indicates several future directions for research on the role of early life adversity in anxiety. Whether elevated fear responding to safe cues mediates the relationship between adolescent adversity and the onset of anxiety disorders is a key test, but it is a test that the present sample unfortunately is underpowered to address. It is clear that larger sample sizes are needed to evaluate this purported mechanistic relationship. One such mechanistic study could include a diagnostic assessment, startle protocol, and administration of the CTI at baseline (thereby reducing the potential biases involved in retrospective recall), followed by subsequent diagnostic assessments during the course of several years. The analysis would focus on whether the relation between adolescent adversity and anxiety disorder onset is mediated by elevated responding during the safe phases of the startle protocol that follow delivery of the aversive stimulus.

Another critical study that draws on this and our previous work is the development of a prevention intervention to modify responding to safety cues among those who experienced adversity in adolescence, particularly if the study proposed in the preceding paragraph does in fact demonstrate that deficits in safety learning mediate the relationship between adolescent adversity and anxiety disorder onset. To identify the target population, researchers could design a prevention program that first assesses adolescents for adverse experiences and then uses a startle protocol or fear-conditioning paradigm to identify which of those individuals who experienced adversity in adolescence also show deficits in safety learning or overresponding to safety cues. Participants could be randomized either to an intervention that aims to train these adolescents to respond differently to safety cues (i.e., training to inhibit fear responding to these cues or an attentional bias modification paradigm to train individuals to attend to safety cues) or to a control group. The design of the study would provide a strong test of whether fear responding to safety cues plays a causal role in the development of anxiety pathology, and if so, the intervention may prevent the onset of anxiety disorders.

Finally, this study uncovered one risk factor for deficits in safety responding, but more-comprehensive models are needed to understand how additional risk factors (such as genetic or other biomarkers) in combination influence deficits in safety responding. Models that include several putative risk factors as main effects as well as their interactions are needed to elucidate which risk factors contribute uniquely to deficits in safety responding. Taken together, research that examines the mechanisms by which early life adversity elevates fear responding to safe cues could inform strategies and targets for prevention interventions.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Notes

1. At risk was defined as either or both biological parents having a current or past diagnosis of a clinically significant anxiety disorder.
2. Pole et al. (2007) referred to the phases in the paradigm as low, medium, and high threat. The procedural elements of these phases are equivalent to the context phase, safe phase, and danger phase, respectively, that are described in other studies.
3. Because it was possible for a participant to complete the first follow-up assessment before completing the startle protocol, we compared the startle protocol dates with the first follow-up SCID-I/NP dates for the six participants we identified as having an Axis I disorder onset at the first follow-up period. In all six cases, the startle protocol was completed before the first follow-up SCID-I/NP, with an average of approximately 5 months between the startle protocol and the first follow-up SCID-I/NP.

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