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High Vagal Tone and Rapid Extinction Learning as Potential Transdiagnostic Protective Factors Following Childhood Violence Exposure

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Abstract

Childhood exposure to violence is strongly associated with psychopathology. High resting respiratory sinus arrhythmia (RSA) is associated with lower levels of psychopathology in children exposed to violence. High RSA may help to protect against psychopathology by facilitating fear extinction learning, allowing more flexible autonomic responses to learned threat and safety cues. In the present study, 165 youth (79 female, ages 9–17; 86 exposed to violence) completed assessments of violence exposure, RSA, and psychopathology, and a fear extinction learning task; 134 participants returned and completed psychopathology assessments two years later. Resting RSA moderated the longitudinal association of violence exposure with PTSD symptoms and externalizing psychopathology, such that the association was weaker among youths with higher RSA. Higher skin conductance responses (SCR) during extinction learning to the threat cue (CS+) was associated with higher internalizing symptoms at follow-up and greater SCR to the safety cue (CS−) was associated with higher PTSD, internalizing, and externalizing symptoms, as well as the p-factor, controlling for baseline symptoms. Findings suggest that higher RSA may protect against emergence of psychopathology among children exposed to violence. Moreover, difficulty extinguishing learned threat responses and elevated autonomic responses to safety cues may be associated with risk for future psychopathology.

Keywords

psychopathology; adolescent; respiratory sinus arrhythmia; aversive learning; childhood trauma

Childhood violence exposure—such as physical abuse, sexual abuse, or witnessing domestic violence—is one of the most pressing public health crises in the world (Kolk, 2017), and explains a substantial portion of mental health problems in the population (Green et al., 2010a; Kessler et al., 2010; McLaughlin et al., 2012). Violence exposure is associated with

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increased risk for many forms of psychopathology across the internalizing and externalizing spectrum (Cicchetti & Toth, 2005; Green et al., 2010; Kessler et al., 2010; McGrath et al., 2017; McLaughlin et al., 2012; Schaefer et al., 2018), as well as with the transdiagnostic general psychopathology factor (i.e., p-factor) (Caspi et al., 2014; Schaefer et al., 2018; Weissman, Guyer et al. 2019). Identifying protective factors that buffer against the onset of psychopathology following childhood exposure to violence is critical to developing more targeted and effective interventions (Duffy et al., 2019).

High vagal tone may be one such protective factor. Vagal tone reflects parasympathetic nervous system (PNS) regulation of heart rate through the vagus nerve (Berntson et al., 1997; Porges, 2007). The vagus nerve acts as a brake on the firing of the sinoatrial node, the heart's primary pacemaker, following activation of vagal motor neurons in the nucleus ambiguus and the dorsal motor nucleus (Allen et al., 2007; Porges, 1995, 2007; Thayer et al., 2009). Respiratory sinus arrythmia (RSA) is a noninvasive measure that reflects vagal tone as variability in heart rate within the frequency band associated with respiration (Allen et al., 2007; Berntson et al., 1993). High vagal tone, indicated by higher levels of RSA at rest, has been shown to moderate the associations of exposure to stress, adversity and violence with psychopathology, such that the link between adversity and psychopathology is weaker or absent in children with high vagal tone (El-Sheikh et al., 2001; Katz & Gottman, 1997; Katz & Gottman, 1995; McLaughlin, Alves, et al., 2014; McLaughlin et al., 2015; Porges, 2007). The specific mechanisms through which high RSA may help to protect against psychopathology following childhood exposure to violence and adversity are unknown. However, one such mechanism could be the way in which vagal tone influences associative learning processes involved in fear extinction.

Extinction learning arises when new associations are formed that compete with those acquired through prior aversive learning (Bouton, 1993; Bouton, 2004; Milad & Quirk, 2012). Aversive learning, or fear learning, occurs when a previously neutral stimulus becomes associated with threat due to repeated pairings with an aversive unconditioned stimulus (US), such as a shock or loud noise. Extinction learning occurs when the conditioned stimulus (CS+), that had previously been paired with the aversive US, is repeatedly presented without the US. During fear extinction learning, repeated presentation of the CS+ in the absence of the US creates a new memory trace associating the CS+ with safety that competes with the original conditioned fear memory (Bouton, 1993; Bouton, 2004; Milad & Quirk, 2012).

Some studies suggest that vagal activity may moderate fear extinction. For example, vagal nerve stimulation has been shown to reduce behavioral indicators of fear (e.g. freezing) responses to the CS+ in animal models (Peña et al., 2013). Alternatively, vagal tone may index central nervous system mechanisms that underlie both vagal activity and fear extinction. Vagal tone has been hypothesized to reflect greater tonic inhibition of the amygdala by the medial prefrontal cortex (mPFC) (Thayer et al., 2012), and mPFC-amygdala coupling has been shown to play an integral role in extinction learning (Giustino & Maren, 2015; Kim et al., 2011; Phelps et al., 2004). Because the inhibitory influence of the mPFC on the amygdala can contribute to both higher vagal tone and the extinction of learned fear responses, higher vagal tone may index a greater capacity for extinguishing

learned fear associations (Beauchaine, 2015; Jennings et al., 2016; Mather & Thayer, 2018; Porges, 2007; Sakaki et al., 2016; Thayer et al., 2012).

The neural circuits involved in fear extinction learning undergo considerable maturation in middle childhood and adolescence (Pattwell et al., 2012). In older adolescents and adults, extinction learning occurs more quickly and recruitment of the mPFC occurs to a greater degree than for children, who recruit the amygdala more strongly for threat and safety learning than adolescents and adults (Lau et al., 2011; Morriss et al., 2019). This developmental shift may be mediated by increasing structural integrity of the uncinate fasciculus—a white matter tract connecting the mPFC and amygdala (Morriss et al., 2019). Lower structural integrity of the uncinate fasciculus in adolescence is associated both with childhood maltreatment and increased internalizing symptoms following exposure to stressful life events (Hanson et al., 2015). Likewise, altered amygdala-vmPFC functional connectivity during fear extinction learning is associated with increased risk for anxiety disorders (Gold et al., 2016). Moreover, altered extinction learning is associated with elevated risk for numerous forms of internalizing psychopathology in adults (Craske et al., 2011; Garcia & Zoellner, 2017; Gazendam et al., 2013; Grillon & Morgan III, 1999; Guthrie & Bryant, 2006; Lissek et al., 2005; Norrholm et al., 2011; Staples-Bradley et al., 2018), as well as children (Britton et al., 2013; Craske et al., 2008; Dvir et al., 2019; Shechner et al., 2015).

Given that smaller physiological responses to the CS+ during extinction learning is associated with decreased risk for PTSD (Blechert et al., 2007; Norrholm et al., 2011; Orr et al., 2000; Peri et al., 2000; Zuj, Palmer, Hsu et al., 2016; Zuj, Palmer, Lommen et al., 2016), and other forms of psychopathology (Craske et al., 2008; McGuire et al., 2016; Michael et al., 2007), higher vagal tone may protect against transdiagnostic psychopathology through associated reductions in fear responses during extinction learning. Indeed, higher resting RSA moderated the association between violence exposure and PTSD avoidance symptoms in children and adolescents in a prior study, such that violence exposure was only associated with elevated symptoms among youths with low resting RSA (Jenness et al., 2019). Higher resting RSA also moderated the association between violence exposure and skin conductance responses (SCR) during early fear extinction, such that, among violence-exposed youths, higher RSA was associated with lower SCR responses to the CS+ during early extinction learning, indicating greater extinction of learned fear. Finally, this pattern of lower SCR during early fear extinction mediated the association between higher RSA and lower PTSD symptoms among youth exposed to violence, suggesting that the protective influence of high vagal tone against PTSD symptoms among youths exposed to violence may operate, at least partially, through enhanced extinction learning (Jenness et al., 2019).

The present study seeks to replicate and extend these findings in a large, longitudinal sample of children and adolescents with high levels of exposure to violence. We evaluate the extent to which vagal tone and fear extinction might promote resilience to trauma-related psychopathology. We first attempt to replicate the findings of Jenness et al. (2019) by conducting analyses in relation to PTSD, a form of psychopathology that is common among children exposed to violence and associated with alterations in extinction learning mechanisms (Milad & Quirk, 2012). We further examined whether vagal tone and fear

extinction act as transdiagnostic mechanisms of resilience by evaluating their associations with internalizing, externalizing, and a measure of general psychopathology (i.e. p-factor). In preregistered analyses (https://osf.io/xur87/). We examine several hypotheses. First, we expected that violence exposure would be positively associated with PTSD, internalizing problems, externalizing problems, and p-factor. Second, we predicted that resting RSA would moderate the association between violence exposure and PTSD, internalizing problems, and p-factor, such that violence exposure would be associated with greater symptoms of psychopathology among youth with low resting RSA, but not among those with high RSA. Third, we hypothesized that larger skin conductance responses (SCR) to the CS+ during early extinction learning would be associated with higher PTSD symptoms, internalizing problems, or p-factor. Fourth, we predicted that resting RSA would moderate the association between violence exposure and SCR to the CS+ during early extinction learning, such that violence exposure would be associated with higher SCR reactivity to the CS+, among youth with low resting RSA, but not among those with high resting RSA. Finally, we predicted indirect effects of violence exposure on PTSD symptoms, internalizing problems, and p-factor via higher SCR reactivity to the CS+ during early extinction, conditional on resting RSA, such that higher SCR reactivity to the CS+ would mediate the association between violence exposure and symptoms of transdiagnostic psychopathology among youths with low resting RSA, but not among youths with high resting RSA. In all analyses of psychopathology, we first examined associations cross-sectionally, and then longitudinally in predicting symptom changes over a two-year follow-up period.

Methods

Participants

Participants were children and adolescents between the ages of 8 and 17 living in the Seattle area. A total of 262 youth aged 8–16 years were enrolled into the study. Youth and caregivers were recruited for participation at schools, after-school and prevention programs, adoption programs, food banks, shelters, parenting programs, medical clinics, and the general community in Seattle, WA between January 2015 and June 2017. Recruitment efforts were targeted at recruiting a sample with variation in exposure to maltreatment-related trauma. To do so, we recruited from neighborhoods with high levels of violent crime, clinics that served a predominantly low-SES catchment area, and agencies that work with families who have been victims of violence (e.g., domestic violence shelters, programs for parents mandated to receive intervention by Child Protective Services). Exposure to violence and other inclusion and exclusion criteria were assessed during the first study visit. Inclusion criteria for the violence-exposed group included exposure to physical or sexual abuse or direct witnessing of domestic violence. Children in the control group were matched to children in the violence-exposed group on age, sex, and handedness; inclusion criteria required an absence of exposure to maltreatment or other forms of significant interpersonal violence. Exclusion criteria included IQ < 80, presence of pervasive developmental disorder, active psychotic symptoms or mania, active substance abuse, and presence of safety concerns. Of the 262 children enrolled in the first study visit, three were excluded from all analysis due to low IQ (n=1), presence of pervasive developmental disorder (n=1), and presence of psychotic symptoms and drug abuse (n=1).

The data on RSA and fear learning were acquired during a second study visit, on a smaller sample of children and adolescents invited to participate in a more involved neuroimaging and physiological assessment. A total of 169 participants participated in the resting electrocardiogram and fear learning tasks at baseline. Equipment malfunctions resulted in loss of all physiological data from four participants. Four participants declined to complete the fear extinction task, and 5 participants discontinued the task before the end of extinction phase. Eleven non-responders during the conditioning phase were dropped from all SCR analyses, as fear extinction learning cannot occur if fear conditioning has not first been established. The full analytic sample for this study consisted of 165 subjects (86 violence-exposed) at the baseline assessment.

A longitudinal follow-up assessment was conducted approximately two years following the baseline assessments (M = 21.96 months, SD = 7.88 months) to assess symptoms of psychopathology. A total of 134 subjects (67 violence-exposed) of the 165 participants with usable data on RSA and fear learning at baseline (79.3%) participated in this follow-up. Of the 31 children in the analytic sample that dropped out, 19 were maltreated (22% attrition), and 12 were not (15% attrition) ($\chi^2 = 0.87$, $p = .350$).

All procedures were approved by the Institutional Review Board at the University of Washington. Written informed consent was obtained from legal guardians; children provided written assent. Maltreatment not previously reported to the relevant authorities was reported to Child Protective Services using standard clinical procedures.

Fear Learning Task

We utilized a fear learning task validated for children and adolescents that included three phases: preconditioning, conditioning, and extinction (McLaughlin et al., 2016; Shechner et al., 2015). During the pre-acquisition phase, participants viewed the CS+ and CS− (blue and yellow bells, counterbalanced across participants, 4 trials each) without the US (an aversive 96 dB alarm noise). The acquisition phase consisted of 20 trials of the CS+ and CS− (10 of each). The CS+ co-terminated with the US in 80% of acquisition trials. During the extinction phase, the CS+ and CS− (8 trials each) were presented without the US. Intervals between trials ranged between 8 to 12 s (mean = 10 s).

Skin conductance responses (SCR) provided the primary metric of fear conditioning. Consistent with Jenness et al. (2019), we focused specifically on responses to the CS+ during the early fear extinction phase of the task, as fear responses tend to return to baseline in the latter half of the extinction task (McLaughlin et al., 2016; Shechner et al., 2015). Moreover, the early extinction phase has been the main focus of studies on extinction learning, and is typically where participants exhibit the greatest variability in fear response intensity during the extinction phase (Milad et al., 2009; Milad & Quirk, 2002).

Measures

Violence Exposure.—As described in more detail previously (Weissman, Jenness, et al., 2019), participants exposed to physical abuse, sexual abuse, or domestic violence were categorized as violence-exposed. Otherwise, they were classified as controls. Children were

classified as experiencing physical or sexual abuse if abuse was endorsed by the child on the Childhood Experiences of Care and Abuse (CECA) interview (Bifulco et al., 1994), PTSD-RI trauma screen, or above the validated Child Trauma Questionnaire (CTQ) threshold (Bernstein et al., 1997; Walker et al., 1999), or by parent on the Juvenile Victimization Questionnaire (JVQ) (Finkelhor et al., 2005), or PTSD-RI trauma screen (Steinberg et al., 2013). Exposure to domestic violence reported on the Violence Exposure Scale for Children-Revised (VEX-R) (Fox & Leavitt, 1995) or PTSD-RI trauma screen was determined based on child report only. Consistency of reporting across these measures is summarized in supplemental materials table S2.

Vagal Tone.—Vagal tone was assessed using noninvasive Electrocardiogram (ECG) recordings, obtained with a Biopac ECG amplifier (Goleta, CA) according to accepted guidelines (Fox & Leavitt, 1995). Participants were instructed to sit quietly without moving for 5 minutes. We used a modified Lead II configuration, placing electrodes on the right clavicle, left lower torso, and right leg (ground). ECG data, sampled at 1.0 kHz, were collected using Biopac MP150 hardware and Acknowledge software. Trained raters, blinded to violence exposure of participants, visually inspected automatic R-peak detection of the ECG data using Mindware Heart Rate Variability (HRV) Software (Mindware Technologies, Gahannah, OH). Visual inspection focused on detecting ectopic beats and confirming accurate detection of R-peaks in the ECG waveform. From IBI time series, we calculated RSA in 1-minute bins. To calculate RSA, the HRV module detrended the data using a first order polynomial to remove the mean and any linear trends, cosine tapered the data, submitted it to Fast Fourier Transformation, and took the natural log integral of high frequency power in the appropriate respiratory frequency band based on participant age (0.24–0.40 Hz for 8–12 years of age, and 0.18–0.40 Hz for 13–16 years of age), (Shader et al., 2018).

Skin Conductance Response.—Skin conductance response (SCR) served as the primary measure of fear extinction learning. For each participant, an experimenter filled two silver/silver chloride electrodes with sodium chloride gel. The tips (fingerprint side) of the participant's non-dominant index and middle finger were exfoliated and wiped with rubbing alcohol, where an experimenter then fastened the two electrodes. We acquired SCR using a Biopac galvanic skin response module (Goleta, CA), which collected skin conductance response at a sampling rate of 250 Hz throughout the fear conditioning task. Using AcqKnowledge 4.0 software (Biopac Systems, Goleta, CA), we calculated SCRs as the difference in amplitude between 1 second pre-CS baseline and peak response to CS+ in the 1–4 seconds following onset of the stimulus in accordance with standard practice (Dawson et al., 2017). The aforementioned 1–4 second response window is a standard procedure used to avoid collecting SCR unrelated to the CS+, and to capture only peak skin conductance response to CS+ (Dawson et al., 2017). In order to ensure that SCR changes during the conditioning phase did not result from the US, the response window terminates before onset of the US. During the conditioning phase of the task, responses were only counted if SCR exceeded 0.02 microsiemens (μs) averaged across trials. Eleven participants were non-responders during the conditioning phase of the task based on this threshold. Eight were from the violence-exposed group, and three were from the control group. These non-

responders were removed from all SCR-related analyses as extinction learning cannot occur if fear conditioning has not first been established. All SCRs from the extinction phase were included in analyses, regardless of their magnitude. Because the residuals from our models using raw SCR amplitudes were skewed (all *S*s > 2.01), we square root transformed the raw SCR amplitudes in order to reduce skew, which is a common approach in developmental fear conditioning studies (Abend et al., 2020; Gamwell et al., 2015; Jovanovic et al., 2014; Kreutzmann et al., 2021; McLaughlin et al., 2016; Morriss et al., 2019; Shechner et al., 2015; Waters & Pine, 2016).

Psychopathology Symptoms

Post-traumatic stress disorder (PTSD) symptoms.—The UCLA Child/Adolescent PTSD Reaction Index (PTSD-RI) is a widely used assessment of PTSD symptom severity with strong convergent validity and internal consistency for the overall measure and among subscales (Jenness et al., 2019; Steinberg et al., 2013). The PTSD-RI measures re-experiencing, avoidance/numbing, and hyper-arousal, which are PTSD symptoms specifically related to childhood exposure to violence. The PTSD-RI has sound psychometric properties (Steinberg et al., 2013) and had excellent internal consistency in our sample (α = .94). The higher of the parent and youth-reported PTSD symptom severity was used in our analyses, consistent with the standard “or” rule for determining the presence of psychopathology symptoms in children (Kessler et al., 2012; Merikangas et al., 2010). PTSD scores at both baseline and follow-up fall within assumptions of normality (*S*=0.702 and *S*=1.212 respectively), and more importantly the residuals of PTSD scores for every model in which PTSD is used fall within assumptions of normality (0.191<*S*s<0.590) (Hair, 2009; Lumley, Diehr, Emerson, & Chen, 2002).

Internalizing and Externalizing Psychopathology.—The CBCL and YSR are among the most sensitive, reliable, and valid scales for measuring parent and child-reported internalizing and externalizing problems. However, these scales are less widely used for assessing symptoms of PTSD, which are common in children exposed to violence, and do not provide the type of in-depth assessment of different domains of anxiety and depression symptoms as other commonly used measures of internalizing symptoms. To assess these symptom domains we use a set of these more comprehensive internalizing measures, including the PTSD-RI, the Children’s Depression Inventory 2 (CDI), and the Screen for Child Anxiety Related Emotional Disorders (SCARED). The CDI is one of the most widely used assessments for depression in the literature, with good test–retest reliability, internal consistency, and construct validity (Rivera et al., 2005; Sitarenios & Kovacs, 1999), particularly over repeated administrations (Finch Jr et al., 1987). The SCARED is a broadly used, validated instrument with good internal consistency, discriminant validity, and test-retest reliability (particularly between depressive and anxiety disorders) used to screen children for anxiety disorders (Birmaher et al., 1997; Birmaher et al., 1999; Hale et al., 2005).

Externalizing symptoms were assessed with the externalizing problems subscale of the CBCL, which is comprised of subscales assessing aggressive behaviors, rule breaking Behaviors, and attention problems. The CBCL is one of the most widely used validated

measures of youth emotional and behavioral problems in both clinical and research settings, and demonstrates strong reliability, as well as convergent and discriminative validity (Achenbach et al., 2003; Ebesutani et al., 2010; Nakamura et al., 2009). The higher of the parent and youth-reported externalizing symptom severity was used in our analyses.

Transdiagnostic Psychopathology.—As described in previous publications (Weissman, Bitran, et al., 2019; Weissman, Jenness, et al., 2019) we performed confirmatory factor analysis (CFA) to test a correlated-factors model specifying Internalizing and Externalizing latent factors. All CFA analyses were performed in MPlus version 8.1 (Muthén & Muthén, 2012). Given that our observed indicator variables were slightly skewed and kurtotic, we used the robust maximum likelihood estimator (MLR), which employs a sandwich estimator to arrive at standard errors robust to non-normality of observations. MLR performs well in modest sample sizes with skewed data, as in the present study (Li, 2016). We assessed the relative fit of each model using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and the Sample Adjusted BIC. Fit indices for the correlated-factors model were: AIC = 6056.31, BIC = 6249.00, Sample adjusted BIC = 6077.79. Standardized factor loadings for the Internalizing (CDI, SCARED, PTSD) latent factor ranged from 0.65 to 0.73, all p's <.001. Standardized factor loadings for the Externalizing (Aggressive Behaviors, Rule Breaking Behaviors, Attention Problem) latent factor ranged from 0.76 to 0.87, all p's < .001 Fit indices for the correlated factors model at follow-up were: AIC = 4507.81, BIC = 4682.09, Sample Adjusted BIC = 4514.19. Standardized factor loadings for the Internalizing Factor ranged from 0.48 to 0.95, all p's <.001. Standardized factor loadings for the Externalizing Factor ranged from 0.76 to 0.84, all p's <.001.

The general psychopathology factor (or p-factor) was estimated in a bi-factor model specifying both a General Psychopathology latent factor ("p") and residual internalizing and externalizing factors. Fit indices for the bi-factor model were: AIC = 6018.23, BIC = 6228.77, Sample adjusted BIC = 6041.71. Standardized factor loadings for the latent p-factor (CDI, SCARED, PTSD, Aggressive Behaviors, Rule Breaking Behaviors, Attention Problems) ranged from 0.44 to 0.80, all p's < .001. Fit indices for the bi-factor model at the longitudinal follow-up were: AIC = 4481.00, BIC = 4665.15, Sample Adjusted BIC = 4487.74. Standardized factor loadings for the latent P factor ranged from 0.46 to 0.81, all p's < .001. For more details, see supplemental materials (Table S1). As assessed by relative fit indices and factor loadings, both the correlated factor model and the bi-factor model fit the data similarly well at the baseline assessment, with a relatively better fit for the bi-factor model.

Data Analysis

Analyses were preregistered, and all data and analysis code are publicly available (osf.io/6hvuy). We deviated from the pre-registration in two instances. First, we incorporated externalizing problems as an additional psychopathology outcome based on a reviewer request. Second, we evaluated whether associations between SCR during early extinction learning and psychopathology were specific to the CS+ or reflect a more general

hyperresponsivity, even to previously learned safety cues, by incorporating analyses of SCR to the CS− during extinction learning.

Analyses were conducted in R Version 3.6.2. All analyses controlled for age, sex, and family income-to-needs ratio, the latter of which differed for youths with and without exposure to trauma. All analyses with psychopathology at follow-up as the outcome controlled for the corresponding measure of psychopathology at baseline.

To evaluate whether vagal tone moderated the association between violence exposure and psychopathology, we estimated linear regression models with violence exposure, RSA, and their interaction in predicting each of the relevant psychopathology outcomes. To examine whether vagal tone moderated the association between violence exposure and SCR to the CS+ during early extinction, we estimated linear regression models with violence exposure, RSA, and their interaction in predicting SCR to the CS+ during early extinction as an outcome. Because SCR was positively skewed, even after square root transformation, asymmetrical bootstrapped confidence intervals were estimated using the “boot” package in R (Canty & Ripley, 2019; Davison & Hinkley, 1997) based on 10,000 bootstrapped samples.

To evaluate whether higher SCR to the CS+ during early extinction was associated with psychopathology, we estimated linear regression models with early extinction SCR to the CS+ in predicting psychopathology outcomes as baseline and follow-up, controlling for violence exposure. To determine whether associations between SCR during early fear extinction learning and psychopathology were specific to the CS+, we also conducted analyses with SCR to the CS− as described above. Specifically, we estimated linear regression models with early extinction SCR to the CS− in predicting psychopathology symptoms at baseline and follow-up, controlling for violence exposure. We examined responses to the threat and safety cues separately because these reflect different psychological processes mediated by distinct neural networks (Fullana et al., 2016). Examining the CS+ at the beginning of extinction provides an index of the degree of responding to the threat cue when – if extinction has occurred – it is no longer is associated with that threat. This response is largely independent from responses to the safety cue that has never been associated with threat. Indeed, we examined skin conductance responses during late acquisition and early extinction and found that they did not significantly differ from one another overall, and the correlation between them was modest (r=.24). We reran our analyses controlling for SCR to the CS+ at the end of acquisition based on reviewer request, and this led to only very small alterations to the magnitude of the nonsignificant interaction between RSA and violence exposure and virtually no change in the magnitude or significance of the association between age and SCR during early extinction or between SCR during early extinction and psychopathology.”

Missing income-to-needs ratio data for 12 participants were handled with multiple imputation, based on 100 imputations using the “mice” package (Buuren & Groothuis-Oudshoorn, 2011).

Results

Descriptive statistics

Demographic information and descriptive statistics for all primary variables for both the violence-exposed and control group can be found in Table 1. Further details on regression analyses can be found in Tables S6–S9 in the supplementary materials.

Violence Exposure and Psychopathology

We first investigated the association of violence exposure with baseline psychopathology. Violence exposure was positively associated with PTSD symptoms, (ß = .67, p < .001), internalizing problems (ß = .53, p < 0.001), externalizing problems (ß = 0.57, p < .001), and the p-factor (ß = 0.62, p < .001) at baseline. When accounting for symptoms at baseline, we did not find any association between violence exposure and PTSD symptoms (ß = .08, p = 0.468), externalizing problems (ß = −.14, p = 0.194), or the p-factor (ß = −.10, p = 0.301) at two-year follow-up. However, we did find an association between violence exposure and fewer internalizing problems at two-year follow-up, when accounting for the higher symptoms at baseline among trauma-exposed youth (ß = −.20, p = 0.048).

RSA, Violence Exposure, and Psychopathology

Resting RSA did not moderate the association between violence exposure and baseline symptoms of PTSD (ß = −0.11, p = .170), internalizing problems (ß = −.09, p = .298), externalizing problems (ß = .04, p = .639), or the p-factor (ß = .00, p = .955). However, resting RSA did moderate the association between violence exposure and PTSD symptoms (ß = −0.20, p = .010), and externalizing problems at two-year follow-up (ß = −0.20, p = .039) (Figure 1). RSA did not moderate the association of violence exposure with either internalizing symptoms (ß = −0.09, p = .340) or p-factor (ß = −.15, p = .078) at two-year follow-up.

RSA, Violence Exposure, and Fear Extinction

Violence exposure was not associated with SCR during the early extinction phase (B = −.01, 95% CI = −.037, .014) and this association was not moderated by RSA (B = −.01, 95% CI = −.028, .022). Thus, we did not proceed with our pre-registered analyses examining extinction learning as a mediator of the link between violence exposure and PTSD symptoms, conditional on RSA. This model did, however, reveal a significant negative association between age and SCR to the CS+ during early extinction (B = −.01, 95% CI = −.011, −.001), indicating that fear extinction learning was greater as age increased. To evaluate the specificity of this association to the learned threat cue, we repeated this analysis with SCR to the CS− as the outcome. There was also a negative association between age and SCR to the CS− during early extinction (B = −.01, 95% CI = −.013, −.001), suggesting that physiological reactivity to the safety cue during early extinction also decreased with age.

Fear Extinction and Psychopathology

Higher SCR to the CS+ during early extinction was associated with higher internalizing symptoms (ß = 0.14, p = .042), but not PTSD (ß = .08, p = .180), externalizing problems (ß

= 0.13, p = .068) or p-factor scores (ß = .12, p = .053) at two-year follow-up (Figure 2). In contrast, higher SCR to the CS− (i.e., safety cue) during early extinction was associated with higher PTSD symptoms (ß = .11, p = .0496), internalizing symptoms (ß = .16, p = .013), externalizing problems (ß = .17, p = .016), and p-factor (ß = .18, p = .004) at the two-year follow-up (Figure 2).

Discussion

This longitudinal study investigated the extent to which vagal tone and autonomic responses during fear extinction learning act as transdiagnostic mechanisms of resilience to psychopathology following childhood exposure to violence. Vagal tone moderated the longitudinal association of violence exposure with PTSD symptoms and externalizing problems, such that the association of violence exposure with psychopathology was lower among youths with high vagal tone than among those with low vagal tone. Greater skin conductance responses to threat cues during fear extinction was associated with higher internalizing symptoms two-years later, whereas elevated skin conductance responses to safety cue during fear extinction was associated with higher symptoms of PTSD, internalizing, and externalizing psychopathology as well as p-factor scores two-years later. However, the protective influence of high vagal tone on the association between violence exposure and psychopathology was not explained by fear extinction learning in this sample.

Vagal tone moderated the longitudinal associations of violence exposure with both PTSD symptoms and externalizing problems, such that violence exposure was associated with worsening symptoms of psychopathology among youth with low RSA, but not among youth with high RSA. These findings replicate findings from a small study examining PTSD symptoms (Jenness et al., 2019) and extends prior work focused on internalizing and externalizing symptoms (El-Sheikh et al., 2001; Jenness et al., 2019; McLaughlin, Alves, et al., 2014; McLaughlin et al., 2015; Porges, 2007), by demonstrating that the association of violence exposure with PTSD symptoms is lower among youth with high RSA than among those with low RSA. These findings align with the Polyvagal Theory, which proposes that high vagal tone enables contextually appropriate autonomic nervous system functioning that promotes greater resilience following exposure to stress and adversity (Porges, 2007; Sullivan et al., 2018). High vagal tone may reflect greater tonic inhibition of the amygdala by the medial prefrontal cortex (mPFC), which plays a critical role in effective regulation of negative emotion (Banks et al., 2007; Thayer et al., 2012). A greater capacity for emotion regulation might be one mechanism through which high vagal tone protects against the emergence of psychopathology following exposure to violence (Edwards & Pinna, 2020; Porges et al., 1994; Weissman, Bitran, et al., 2019).

Higher sympathetic nervous system (SNS) reactivity to both threat and safety cues during extinction learning was associated with subsequent increases in transdiagnostic psychopathology. Specifically, higher SCR to learned threat cues during early extinction learning predicted higher internalizing symptoms two years later. Elevated physiological reactivity to threat cues may reflect persistent fear to cues that were previously associated with threat that contributes to increased risk for internalizing problems in youth. Indeed, prior work suggests that heightened SNS responses to threat cues during early extinction

learning is associated with increased risk for anxiety disorders in children (Craske et al., 2008). The present study extends these findings by demonstrating that higher SCR to learned threat cues during early extinction learning is associated with a broad range of internalizing problems in a longitudinal design. However, this association was not specific to learned threat cues. Higher SCR to learned safety cues during early extinction learning was associated with higher symptoms of PTSD, internalizing problems, externalizing problems, and general psychopathology two years later. Poor threat–safety discrimination during fear conditioning has been associated with externalizing psychopathology in children and adolescents in cross-sectional studies (Fairchild et al., 2008; McLaughlin et al., 2016). To our knowledge, the present study is the first to link heightened SNS responses to the threat and safety cues during extinction learning with internalizing, externalizing, and general psychopathology (p-factor) in youth. This pattern of increased reactivity following fear learning, to both learned threat and safety cues is consistent with the recently proposed "better safe than sorry" information processing strategy (Bergh et al., 2020). This strategy in the context of aversive learning is thought to reflect oversimplified perception of stimulus features (e.g. recognizing the bell's shape but not its color) that may lead one to expect that situations containing features of learned threat cues (e.g. the bell's shape) are dangerous, even if these situations also contain features that designate safety (e.g. the bell's color) (Bergh et al., 2020). This "better safe than sorry" information processing strategy may result in chronic deviations of expectations from reality that lead to greater levels of psychopathology (Bergh et al., 2020). In situations indicative of safety, failure to differentiate between threat and safety cues may result in contextually inappropriate fear responses that contribute to increased risk for multiple forms of psychopathology in youth, ranging from anxiety and internalizing problems to reactive aggression. While these findings related to the safety cue provide important context about the specificity of associations between responses to the conditioned threat cue and psychopathology, analyses related to the CS− were not preregistered, and thus should be considered preliminary until replicated in future studies.

We also found a negative association between age and SNS responses to both threat and safety cues. This suggests that the neural systems involved in extinguishing learned threat responses are continuing to develop across childhood and adolescence. Indeed, SCR during extinction learning tends to be higher in children than adults (Britton et al., 2013). Thus, heightened reactivity to threat and safety cues among youth with psychopathology may reflect altered maturation of processes involved with fear extinction learning, including perceptual memory and the regulation of SNS activity (Bergh et al., 2020; Britton et al., 2013). Indeed, developmental change in fear extinction learning may be most pronounced during childhood and adolescence (Pattwell et al., 2012), suggesting this may be a period in which the mechanisms underlying threat and safety learning are particularly susceptible to environmental influences. These findings underscore the need for further research examining the influence of threat and safety learning on psychopathology across development.

Neither vagal tone, violence exposure, nor their interaction were associated with fear extinction learning. Thus, we failed replicate the finding that enhanced fear extinction learning may be a mechanism through which vagal tone protects against psychopathology in children exposed to trauma (Jenness et al., 2019). We also failed to replicate the

prior finding that vagal tone moderates the association between violence exposure and psychopathology cross-sectionally. This could be because past cross-sectional studies examining such associations, on average, used samples comprised largely of adolescents (Jenness et al., 2019; McLaughlin et al., 2014, 2015). Developmental differences in vagal tone might arise as a result of increasing inhibition of the amygdala by the mPFC with age, a pattern consistent with a number of studies on functional connectivity of the mPFC and amygdala (Gee et al., 2013; Gentzler et al., 2012; Weissman, Guyer et al., 2018, 2019), albeit in different types of emotion processing tasks than the aversive learning task utilized here. The link between vagal tone and enhanced extinction learning in violence-exposed youth may therefore depend on the maturation of this brain circuit. Thus, it is possible that the protective influence of vagal tone manifests differently across development as the neural circuits that underlie threat and safety learning mature.

Our findings underscore the need for future research investigating whether interventions that target vagal tone might also mitigate the effects of exposure to violence in youth. For example, mindfulness-based interventions, which have been shown to increase vagal tone in response to laboratory stressors, have also been shown to reduce symptoms of psychopathology among adults exposed to interpersonal violence (Ditto et al., 2006; Gallegos et al., 2015; Kelly & Garland, 2016). However, we are unaware of work demonstrating the effectiveness of interventions on psychopathology that strengthen vagal tone in youth. Thus, future research should explore, for example, whether interventions that are personalized to this developmental period and target threat and safety learning in a more scaffolded manner (e.g. mindfulness-based interventions) enhance the effectiveness of exposure-based treatments (Björkstrand et al., 2019; Gard et al., 2014; McGuire & Storch, 2019; Pattwell et al., 2012; Sullivan et al., 2018).

Limitations

The current study has several limitations. First, differences in aversive learning have been observed in children exposed to trauma and thus differences in extinction learning may also partially reflect differences in the patterns of learning of conditioned fear (Fairchild et al., 2008; McLaughlin et al., 2016). Furthermore, socioeconomic status is confounded with exposure to violence in our sample. While we include family income as a covariate in our analyses, future studies that more carefully match on socioeconomic status may extend this work to further disentangle the unique influence of this environmental factor on psychopathology. Also, given that exposure to violence in our sample predates measures of vagal tone, we are unable to establish the extent to which individual differences in vagal tone may be a protective factor that exists before exposure to trauma or may reflect differential trajectories of physiological adaptation or calibration following trauma (Giudice et al., 2011). Future research using genetically controlled and/or multi-wave longitudinal designs are necessary to further understand how development of vagal tone influences psychopathology among children exposed to adversity. Furthermore, we acknowledge that a bi-factor model can only accurately uncover the underlying of structure in the general population using large samples, and even then, whether the bifactor model actually best represents the true structure of psychopathology is a matter of considerable disagreement and mounting controversy in the field (Burns et al., 2020; Heinrich et al., Pre-Print; Levin-

Aspenson et al., 2020). However, this was not our intent or aim in the present analysis. Consistent with other similar studies comparing children with and without exposure to adversity on p-factor (Schaefer et al., 2018; Wade et al., 2018), we use the bi-factor model primarily to condense an array of disparate psychopathology symptoms into a single transdiagnostic factor (p-factor) for use in subsequent analyses. Our goal is to examine how violence exposure, RSA, and extinction learning are associated with a measure of transdiagnostic psychopathology symptoms, not to estimate the structure of psychopathology in our sample.

Conclusion

We examined the role of fear extinction learning and high vagal tone as potential protective factors for psychopathology among youths exposed to violence. We found that the longitudinal association of violence exposure with PTSD symptoms and externalizing problems was weaker among children with high vagal tone than among those with low vagal tone. These associations were not explained, however, by differences in extinction learning. We also provide novel evidence that the magnitude of SNS responses to learned threat and safety cues decrease with age, suggesting developmental improvements in extinction learning, and that greater SNS reactivity to both threat and safety cues may contribute to transdiagnostic psychopathology over time. Altered maturation of processes involved in threat and safety learning may increase risk for psychopathology as children grow older and require more refined information processing strategies and contextually appropriate autonomic nervous system functioning in order to adapt to new environments and function with greater independence. Taken together, these findings suggest that interventions that target increasing vagal tone, while also decreasing reactivity to learned threat and safety cues in a developmentally appropriate manner, may have potential to enhance the effectiveness of current evidence-based treatments and prevention efforts for psychopathology in youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The data that support the findings of this study are openly available in the Open Science Framework at https://doi.org/10.17605/OSF.IO/XUR87 (Susman, Weissman, & McLaughlin, 2020).

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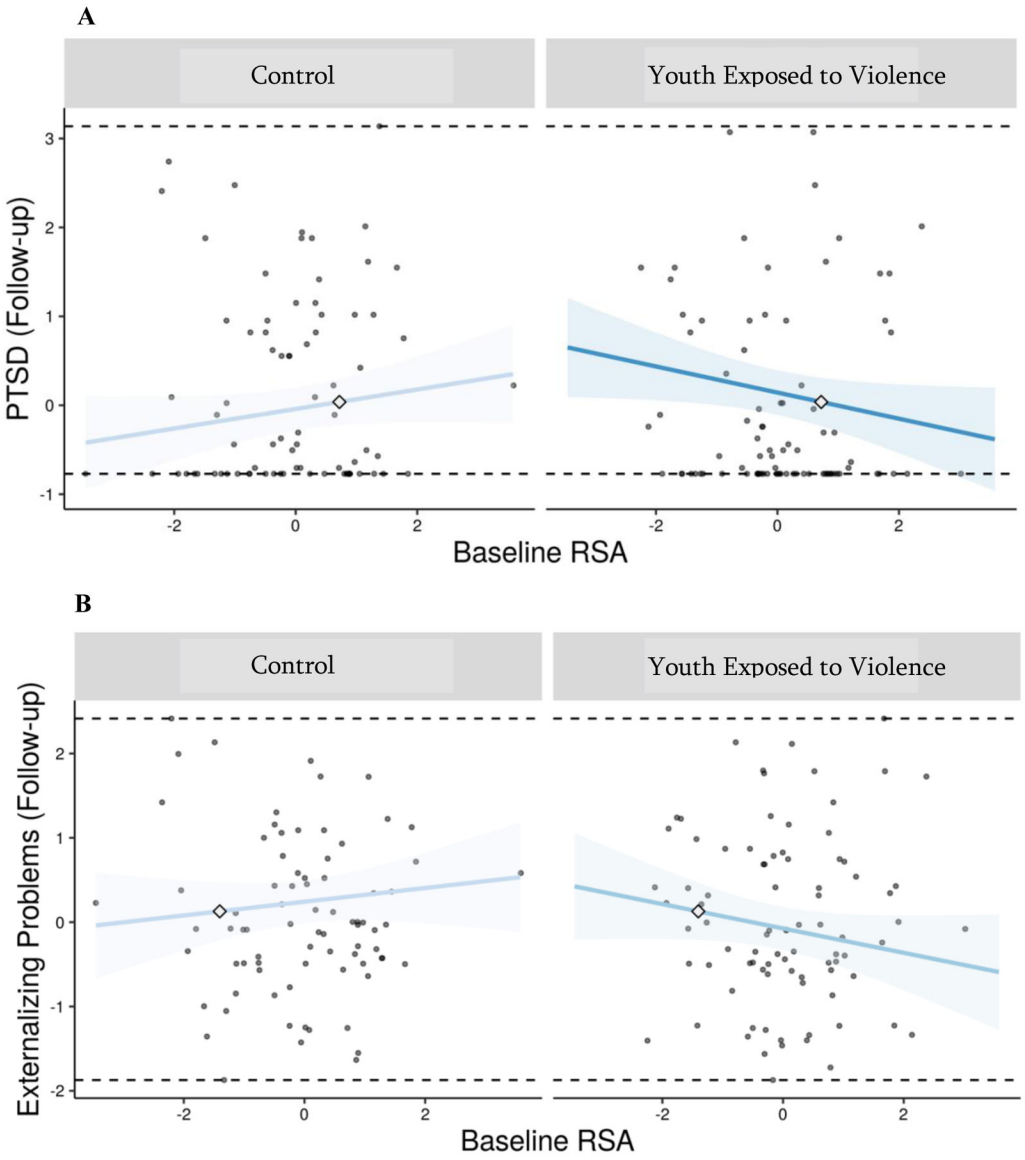

Figure 1.

A) The association between baseline respiratory sinus arrhythmia (RSA) and PTSD symptoms at two-year follow-up in violence-exposed, and unexposed youth. B) The association between baseline RSA and externalizing problems at two-year follow-up, in violence-exposed, and unexposed youth.

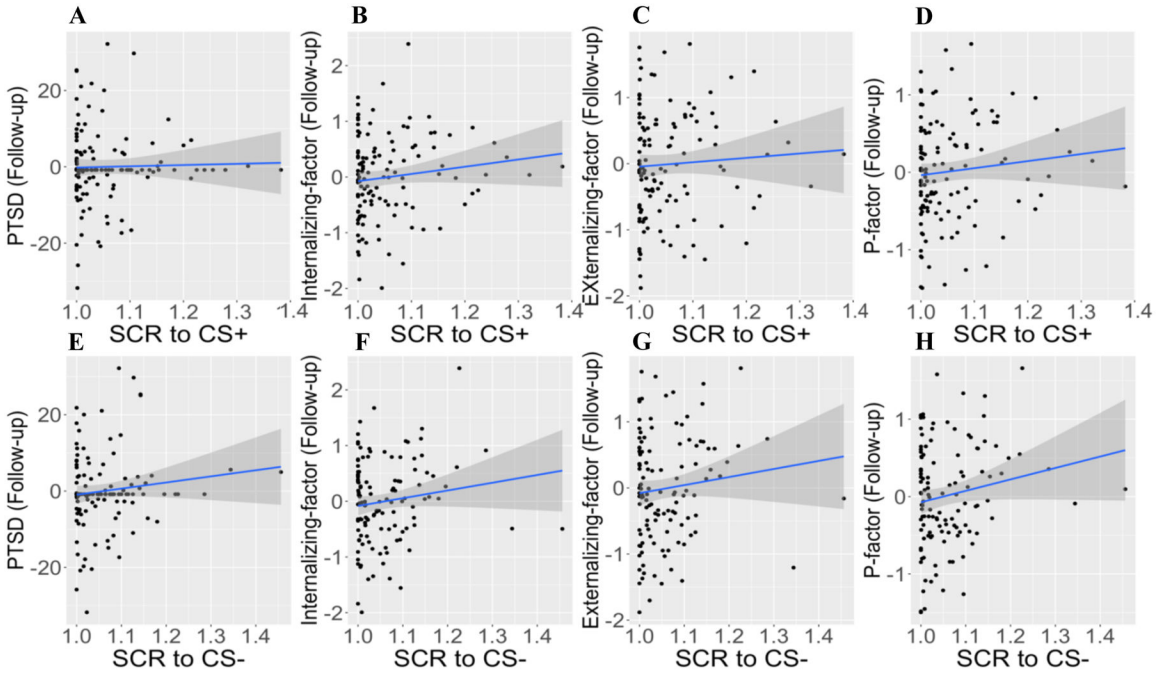

Figure 2.

A) Higher SCR to the CS+ during early extinction learning did not predict higher PTSD symptoms at follow-up, controlling for baseline (B = 16.84, ß = .08, SE = 12.48, t = 1.35, p = .180). *B)* Higher SCR to the CS+ during early extinction learning predicted higher internalizing problems at follow-up, controlling for baseline (B = 1.86, ß = 0.14, SE = 0.13, t = 2.06, p = .042). *C)* Higher early extinction SCR to the CS+ marginally predicted higher externalizing problems at follow-up, controlling for baseline (B = 1.78, ß = 0.13, SE = 0.97, t = 1.85, p = .068). *D)* Higher early extinction SCR to the CS+ marginally predicted higher p-factor at follow-up, controlling for baseline (B = 1.58, ß = .12, SE = 0.81, t = 1.94, p = .053). *E)* Higher early extinction SCR to the CS− predicted PTSD symptoms at follow-up, controlling for baseline (B = 24.20, ß = .11, SE = 12.19, t = 1.98, p = .0496). *F)* Higher early extinction SCR to the CS− predicted higher internalizing-factor at follow-up, controlling for baseline (B = 2.23, ß = .16, SE = 0.88, t = 2.54, p = .013). *G)* Higher early extinction SCR to the CS− predicted higher externalizing problems at follow-up, controlling for baseline (B = 2.29, ß = .17, SE = 0.94, t = 2.44, p = .016). *H)* Higher early extinction SCR to the CS− predicted higher p-factor at follow-up, controlling for baseline (B = 2.31, ß = .18, SE = 0.78, t = 2.96, p = .004).

Table 1

Descriptive statistics by violence exposure.

	Exposed to Violence (n = 86)		Controls (n = 79)			
	%	N	%	N	χ^2	P-value
Sex					1.08	.300
Female	52.3	45	43	34		
Male	47.7	41	57	45		
	M	**(SD)**	**M**	**(SD)**	**t-Value**	**P-value**
Income to Needs	2.22	2.28	5.39	2.26	8.64	<.001
Age	12.71	2.74	12.61	2.58	−0.22	.825
PTSD (Baseline)	29.15	15.55	3.95	8.81	−12.94	<.001
PTSD (Follow-up)	21.52	14.94	1.90	6.51	−9.80	<.001
Internalizing (Baseline)	0.54	0.75	−0.62	0.69	−10.36	<.001
Internalizing (Follow-up)	0.36	1.03	−0.30	0.76	−4.219	<.001
P-factor (Baseline)	0.53	0.67	−0.67	0.69	−11.28	<.001
P-Factor (Follow-up)	0.41	0.91	−0.39	0.71	−5.69	<.001
Resting RSA	5.91	1.10	5.83	1.18	−0.49	.622
Early Extinction CS+	1.04	0.07	1.06	0.08	1.99	.049
Early Extinction CS−	1.06	0.08	1.06	0.06	0.25	.803

Note: RSA = respiratory sinus arrhythmia; CS + = conditioned stimulus paired with aversive noise; PTSD = posttraumatic stress disorder.