Dimensions of Adversity, Physiological Reactivity, and Externalizing Psychopathology in Adolescence: Deprivation and Threat

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ABSTRACT

Objective: Dysregulation of autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis function is a putative intermediate phenotype linking childhood adversity (CA) with later psychopathology. However, associations of CAs with autonomic nervous system and HPA-axis function vary widely across studies. Here, we test a novel conceptual model discriminating between distinct forms of CA (deprivation and threat) and examine their independent associations with physiological reactivity and psychopathology.

Methods: Adolescents ($N = 169$; mean [SD] age, 14.9 [1.4] years) with a range of interpersonal violence (e.g., maltreatment, community violence) and poverty exposure participated in the Trier Social Stress test (TSST). During the TSST, electrocardiogram, impedance cardiograph, salivary cortisol, and dehydroepiandrosterone-sulfate data were collected. We compared the associations of poverty (an indicator of deprivation) and interpersonal violence (an indicator of threat) on sympathetic, parasympathetic, and HPA-axis reactivity to the TSST, and assessed whether these differences mediated the association of adversity with internalizing and externalizing symptoms.

Results: Exposure to poverty and interpersonal violence was associated with psychopathology. Interpersonal violence, adjusting for poverty, was associated with blunted sympathetic (b = 1.44, $p = .050$) and HPA-axis reactivity (b = −.09; $p = .021$). Blunted cortisol reactivity mediated the association of interpersonal violence with externalizing, but not internalizing, psychopathology. In contrast, poverty was not associated with physiological reactivity after adjusting for interpersonal violence.

Conclusions: We provide evidence for distinct neurobiological mechanisms through which adversity related to poverty and interpersonal violence is associated with psychopathology in adolescence. Distinguishing distinct pathways through which adversity influences mental health has implications for preventive interventions targeting youths exposed to childhood adversity.

Key words: interpersonal violence, poverty, physiological reactivity, externalizing disorders, psychopathology.

INTRODUCTION

Childhood adversities (CA) exert a profoundly deleterious impact on development, contributing to population-wide disparities in mental health, educational attainment, and economic productivity (1). Nearly 60% of US adolescents report experiencing at least one adversity, including maltreatment, poverty, parental death, or divorce (2). Epidemiological and clinical studies indicate that children exposed to CAs are at elevated risk for a wide spectrum of internalizing and externalizing problems, including depression, anxiety, disruptive behavior, and substance use disorders (2,3). Consequently, CAs represent salient environmental risk factors that imperil successful adjustment across multiple domains.

The past decade has witnessed a burgeoning interest in how CAs shape neurobiological development, leading to elevated risk for psychopathology (4). In particular, conceptual models propose that prolonged activation of physiological systems after chronic adversity results in a disruption of

CA = childhood adversity, **DHEA-S** = dehydroepiandrosterone sulfate, **ECG** = electrocardiogram, **HPA** = hypothalamic-pituitary-adrenal, **PEP** = pre-ejection period, **PNS** = parasympathetic nervous system, **SNS** = sympathetic nervous system, **TSST** = Trier Social Stress Test

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stress regulatory systems in the body (5). The autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis operate synergistically to orchestrate physiological responses to environmental stressors, driving long-term biological adaptations necessary for learning and survival (6). The sympathetic (SNS) and parasympathetic (PNS) branches of the ANS play an important role in maintaining the body's homeostatic balance in the face of immediate stressors (i.e., activating the "fight or flight" response) through changes in cardiovascular tone (7). In contrast, the HPA-axis maintains homeostasis by modulating levels of slower-acting hormones (e.g., cortisol) in the bloodstream (8).

Anomalies in ANS and HPA-axis function have been documented after exposure to CAs spanning maltreatment (9), poverty (10,11), institutionalization (12), parental loss (13), and parental depression (14). However, the interpretation of this literature is complicated by the lack of a clear physiological profile associated with CA exposure. Whereas some studies document dysregulated (hyporesponsive and hyper-responsive) autonomic and neuroendocrine response to psychosocial stressors after adversity (12,15–17), others find discordance between autonomic and neuroendocrine responses (18), or no differences in physiological reactivity at all (19).

These divergent findings may be accounted for, in part, by variability in the types of CA investigated in prior human studies (20–22). To date, studies of CA in humans have typically focused on the effects of single forms of adversity (e.g., maternal education) that are confounded with other unmeasured exposures, such as maltreatment or community violence exposure (23). An alternative approach has been to examine associations between the number of adverse childhood experiences (e.g., adverse childhood experiences scores) and subsequent endocrine and cardiovascular response to stress (24,25). Neither of these approaches assesses whether specific domains of exposures result in specific patterns of ANS and HPA-axis development.

In the present study, we test a recent theoretical model that predicts variability in neurodevelopment after CA exposure (26,27). The model proposes two orthogonal dimensions of early experience, each having distinct effects on brain and biological systems: (i) *deprivation*, referring to exposures that reflect the absence of expected environmental inputs, and common in the case of neglect, poverty, or institutionalization, and (ii) *threat*, referring to interpersonal violence exposures that involve harm or threat of harm to the child, such as physical and sexual abuse or direct exposure to community violence. Importantly, both types of experience contribute to psychopathology (28), and research attempting to find specificity among types of CA and risk for internalizing and externalizing psychopathology has largely failed (see, e.g., McMahon et al. (29) for a review). However, the model predicts that deprivation and threat have differential impacts on the intervening neurobiological processes that underlie differences in psychopathology.

Specifically, evidence from human and animal studies suggests that threat exposure influences the development of corticolimbic circuits that underlie fear learning and salience processing (30), thereby modifying physiologic responses to novel stressors (15). In rodents, exposure to threat early in development results in prolonged alteration in amygdala, hippocampal, and medial prefrontal cortex (mPFC) functions in response to subsequent threat cues (31), as well as hyperreactivity of the HPA-axis (32). The amygdala, hippocampus, and mPFC modulate behavioral and physiological responses to environmental threats via projections to the hypothalamus and brainstem (33). The amygdala signals the hypothalamus to stimulate the release of corticotrophin releasing hormone, triggering a cascade of neurochemical events that culminates in the release of cortisol by the adrenal cortex. Perception of environments threats also engages the SNS and PNS by innervating neural fibers in the brain stem (34). Human studies of interpersonal violence exposure mirror findings in animals, revealing that these exposures in childhood are associated with ANS and HPA-axis dysfunction (35,36) and disruption in function and structure of the hippocampus, amygdala, and mPFC (37–39). Given the human and animal evidence, we hypothesize that experiences of threat will be associated with disruptions in physiological reactivity after adjusting for deprivation.

In contrast, we hypothesize that poverty, a proxy for deprivation, is unlikely to result in disrupted physiological reactivity after adjusting for threat. Although several studies have demonstrated associations between poverty and physiological reactivity indicators in children and adolescents (11,40–42), these studies did not account for co-occurring exposure to threat, such as interpersonal violence. Children living in poverty are at higher risk for exposure to many forms of interpersonal violence, including maltreatment (43,44), intimate partner violence (45), and community violence (46). Although some studies examining the impact of interpersonal violence exposure on physiological reactivity have controlled for poverty or socioeconomic status (23,36,47), almost no investigations of the impact of poverty on physiological reactivity have controlled for interpersonal violence. The purpose of the current study, then, was to test these hypothesized associations between threat (adjusting for deprivation) and deprivation (adjusting for threat) with autonomic (SNS and PNS) and neuroendocrine (salivary cortisol and dehydroepiandrosterone sulfate [DHEA-S]) responses to a laboratory stressor.

Notably, we use the ratio of cortisol to DHEA-S as a measure of HPA-axis function. Whereas cortisol has been extensively studied in the stress literature, DHEA and its sulfate, DHEA-S, have received considerably less attention (48). Evidence suggests that these steroids have

antiglucocorticoid properties and may therefore counterbalance the effects of cortisol on stress-induced neurotoxicity (49). Accordingly, it has been suggested that the ratio of cortisol to DHEA may represent a better index of neuroendocrine imbalance than cortisol alone (50).

Next, given the robust associations between CA exposure and psychopathology (2), we examined whether effects of CAs on internalizing and externalizing symptoms were mediated by physiological reactivity. A robust research literature suggests that alterations in HPA-axis or ANS function are associated with both internalizing and externalizing difficulties in childhood and adolescence. Youth with internalizing problems generally exhibit elevated cortisol (51) and SNS (52) response to psychosocial stress, whereas externalizing problems are characterized by blunted ANS arousal and HPA-axis reactivity (53,54). Together, these data suggest that both hyperactivation and hypoactivation of physiological systems are associated with risk for later psychopathology.

Threat exposure was operationalized as exposure to physical abuse, sexual abuse, or direct exposure to community violence. Poverty was operationalized as whether or not a family's income fell above or below the federal poverty line. Although poverty is not a direct measure of deprivation (i.e., it is possible to be poor and still have exposure to enriched cognitive, social, and linguistic inputs), low parental SES has been associated with exposure to fewer enriched cognitive experiences in childhood (55) including impoverished linguistic inputs and decreased overall exposure to language (56,57). As such, poverty serves as a proxy for deprivation exposure in this study. Consistent with the deprivation/threat model, we hypothesized that whereas deprivation and threat would be associated with internalizing and externalizing psychopathology, only threat exposure (adjusting for deprivation) would influence physiological reactivity, and in turn statistically mediate associations with psychopathology.

METHODS

Sample

A sample of 169 adolescents (75 males and 94 females) was recruited from schools, after-school programs, medical clinics at Boston Children's Hospital, and the wider community in Boston and Cambridge, MA, between July 2010 and November 2012. Recruitment sites were selected to oversample diverse ethnic/racial groups and those with experiences of childhood adversity (i.e., participants were recruited from neighborhoods with high levels of community violence and from clinics that served a predominantly low-SES catchment area). The sample had a mean (SD) age of 14.9 (1.4) years. The sample was racially diverse: 41.3% white (n = 69), 18.0% black (n = 30), 18.0% Hispanic/Latino (n = 30), 7.8% Asian (n = 13), and 15% biracial/other (n = 25). All females were postmenarchal. Twenty six percent of participants came from households whose income fell below the federal poverty line (n = 42), and approximately one third of the sample (38.3%; n = 64) was from single-parent households. Participants were excluded from the study if they were currently using corticosteroids. Two participants declined to participate in the psychosocial stress task, resulting in an analytic sample of 167 participants. Parents provided informed consent, and adolescents provided assent. All study procedures were approved by the institutional review boards at Boston Children's Hospital and Harvard University.

Procedure

Participants completed the Trier Social Stress Test (TSST), a widely used stress induction procedure used with children and adolescents (58). Participants arrived to the laboratory with their parents, and written consent and assent were obtained from parents and adolescents, respectively. After providing saliva samples, participants completed a five-minute baseline period in which they sat quietly while physiological data (SNS and PNS) were acquired. Then, adolescents completed questionnaire and interview measures assessing adversity exposure and psychopathology. Next, after a second five-minute baseline period, participants completed three tasks in front of two experimenters: a speech preparation period, a five-minute speech to experimenters, and a mental subtraction task (36). Throughout all phases of the TSST (baseline, speech preparation, and speech, math), participants were seated, and continuous cardiac measures were recorded noninvasively. Saliva samples were acquired at two time points: (1) immediately before the initial resting period, 20 to 30 minutes after participants had arrived at the laboratory; and (2) 15 minutes after the beginning of the speech portion of the TSST. Subjects were instructed to refrain from exercising, eating, or drinking caffeinated beverages within four hours of their study visit. To account for potential diurnal effects on the HPA-axis, all participants started the laboratory session in the afternoon (between 1:00 and 4:00 PM).

Autonomic Measures

Electrocardiogram (ECG) recordings were acquired using a Biopac ECG amplifier (Goleta, CA), using a modified Lead II configuration (right clavicle, left lower torso, and right leg ground). Cardiac impedance was obtained using a Bio-Impedance Technology model HIC-2500 impedance cardiograph (Chapel Hill, NC). Electrodes were placed on the neck and torso. Electrocardiogram and impedance cardiography data were sampled at 1.0 kHz and acquired using Biopac MP150 hardware and Acqknowledge software. Data were scored by trained research assistants blind to participant identity and were averaged into one-minute epochs using Mindware Heart Rate Variability software (Mindware Technologies, Gahanna, OH).

Respiratory sinus arrhythmia (RSA) was used as a measure of PNS reactivity and was calculated from the inter-beat interval time series using spectral analysis implemented in Mindware. Respiratory sinus arrhythmia was calculated for the high-frequency band 0.12 to 0.40 Hz. To ensure that RSA represents a measure of pure parasympathetic cardiac control, respiration rate was derived from the basal cardiac impedance signal and included as a covariate in all PNS analyses. Greater PNS reactivity is indicated by a task-related decrease in RSA from basal levels (i.e., vagal withdrawal).

Pre-ejection period (PEP) was calculated from impedance cardiography data as a measure of SNS reactivity. Pre-ejection period represents the time interval beginning with ventricular depolarization and ending when blood is ejected from the left ventricle, where shorter intervals correspond to greater SNS activation (59). As scoring of impedance cardiography data requires manual placement of the B point (the opening of the aortic valve), these data were independently scored by two raters, and differences of more than 5% were adjudicated by one of the study investigators (K.M.).

Neuroendocrine Measures

Cortisol (nmol/L) and DHEA-S (ng/mL) concentrations were collected at three time points during the TSST. Neuroendocrine samples were obtained with Cryovial tubes (Immuno-Biological Laboratories, Hamburg, Germany) using the drool method, whereby participants expectorate approximately 1.5 mL of saliva into a Cryovial with a plastic straw. Saliva samples were

stored immediately at −20°C until they were shipped on dry ice to a laboratory in Boston, Massachusetts. Samples were assayed for cortisol and DHEA-S using commercially available luminescence immunoassay kits (commercially available luminescence immunoassay; Immuno-Biological Laboratories, Hamburg, Germany). Intra-assay and interassay coefficients of variance were acceptable (cortisol, 4.24% and 3.34%; DHEA-S, 3.96% and 4.33%, respectively). Hypothalamic-pituitary-adrenal-axis activity was calculated by dividing cortisol by DHEA-S for each time point.

Self-Report Measures

Interpersonal violence exposure was assessed using two self-report questionnaires. First, the Childhood Trauma Questionnaire (60) is a 28-item self-report measure that retrospectively assesses five types of negative childhood experiences. Participants respond to each item in the context of "while growing up" on a five-point Likert scale ranging from "never" to "very often". Fifteen items corresponding to emotional abuse (e.g., "people in my family said hurtful or insulting things to me"), physical abuse (e.g., "I got hit so hard by someone in my family that I had to see a doctor or go to the hospital"), and sexual abuse (e.g., "someone molested me") were summed to generate an overall index of childhood abuse ($\alpha = .90$). We also administered the Screen for Adolescent Violence Exposure (61), a 32-item measure of adolescents' exposure to direct or indirect violence in school, home, or neighborhood contexts. We summed all 12 items corresponding to direct violence exposure (e.g., "someone has pulled a knife on me"), measured on a five-point Likert scale ranging from "never" to "almost always" ($\alpha = .89$). Finally, we *z*-transformed and summed the Childhood Trauma Questionnaire and Screen for Adolescent Violence Exposure measures ($r = .23$; $p < .001$) to create an overall interpersonal violence exposure composite, with higher scores indicating greater exposure to interpersonal violence.

Deprivation. The ratio of income to needs was computed by diving parent-reported family income by the federal poverty thresholds (as determined by the number of people in the household). Our primary measure of deprivation was a dichotomous variable indicating whether participants lived under the federal poverty line (i.e., an income-to-needs ratio <1). For sensitivity analyses, we also treated deprivation as a continuous measure by taking a log transformation of income-to-needs ratio (62).

Psychopathology was assessed using the Youth Self-Report form from the Child Behavior Checklist (63). The Child Behavior Checklist is a widely used measure of youth emotional and behavioral problems and has been population-normed to generate age-standardized estimates of psychopathology. Here, we use the global externalizing and internalizing subscales of the YSR.

Data Analysis

A log transformation was used to normalize the distribution of cortisol/DHEA-S before analysis.

Autonomic reactivity to the TSST was modeled by predicting values of PEP and RSA measured during the first minute of the speech and math portions of the TSST while adjusting for these parameters during the first minute of baseline. Similarly, neuroendocrine reactivity was modeled by predicting cortisol/DHEA after the speech, adjusting for baseline levels. Multiple regression models were conducted with the *sem* package in Stata 13.1 (StataCorp, College Station, TX), using full information maximum likelihood to account for occasional missing data due to noise in the ANS waveforms, equipment malfunctions, etc. Less than 8% of the data were missing on any one variable. Following Little (64), data were determined to be missing completely at random.

We used standard tests of mediation (65) to determine whether physiological reactivity mediated the association between our two adversity measures (poverty and interpersonal violence) and psychopathology. First, we tested associations between the predictors (interpersonal violence and poverty) and the outcomes (internalizing and externalizing symptoms) (C path). Interpersonal violence and poverty were entered in separate regression models and then included together. Next, we tested the association between the predictors and the proposed mediators (PEP, RSA, and cortisol/DHEA during the speech and math portions of the TSST) (A path). As previously mentioned, interpersonal violence and poverty were entered separately and then together. Finally, we tested associations between the mediators and the outcomes (B path). If these criteria were met for a single path, the significance of the indirect path (through the mediator) was tested using a bootstrapping approach (66). This approach generates bias-corrected, bootstrapped confidence intervals for total and specific indirect effects of the predictors, on the outcome, through the mediators. Confidence intervals that do not include zero indicate statistically significant mediation. Age and sex were included as covariates in all models, and respiration rate was included as a covariate for all models using RSA. Unstandardized regression weights are presented in the results.

RESULTS

Physiological Reactivity

We first examined task-related changes in physiological reactivity from baseline using paired sample *t* tests. Significant increases in SNS activity (i.e., smaller PEP than baseline) were observed for 90% of participants for the speech ($t = 13.78$; $p < .001$) and 82% of participants for the math ($t = 11.52$; $p < .001$) portions of the TSST. Similarly, vagal suppression (i.e., smaller RSA than baseline) was observed for 70% of participants for speech ($t = 6.29$; $p < .001$) and 61% of participants for math ($t = 4.25$; $p < .001$). Finally, increased HPA-axis reactivity (i.e., greater cortisol:DHEA-S than baseline) occurred in 78% of participants ($t = 7.06$; $p < .001$).

Adversity Exposure and Psychopathology

Table 1 displays means and standard deviations for key study variables. Bivariate correlations are presented in Table 2. After examination of the uncontrolled, bivariate associations, we ran multiple regression models testing the association between CAs (poverty and violence exposure) and internalizing and externalizing psychopathology. Poverty was associated with externalizing (b = 4.74; $p = .005$), but not internalizing symptoms (b = 2.40; $p = .18$). Children whose household income fell below the federal poverty line exhibited greater levels of externalizing symptoms than those above the poverty line. This pattern of results did not change when adjusting for violence exposure. Exposure to violence was significantly associated with both externalizing (b = 3.06; $p < .001$) and internalizing symptoms (b = 2.87; $p < .001$), which did not change when adjusting for poverty. Children with greater exposure to violence had higher levels of psychopathology.

Adversity Exposure and Physiological Reactivity

Figure 1 displays SNS, PNS, and HPA-axis reactivity to the TSST, by poverty and interpersonal violence exposure. Analysis of baseline physiological data revealed that poverty was associated with significantly higher baseline HPA-axis activity (b = .60; $p = .013$) and marginally higher baseline PNS activity (b = .46; $p = .065$). In contrast, no

TABLE 1. Distribution for Childhood Adversity, Physiological Reactivity, and Psychopathology Variables (N = 167)

Variable	Mean	SD
SAVE traumatic violence	13.40	2.57
CTQ abuse	19.64	7.03
RSA - baseline	6.92	1.34
RSA - speech	6.03	1.41
RSA - math	6.38	1.43
PEP - baseline	102.61	14.77
PEP - speech	86.39	19.58
PEP - math	90.99	18.30
Cortisol - baseline	6.59	6.00
Cortisol – after speech and math	10.98	8.09
DHEA-S – baseline	16.61	34.62
DHEA-S – after speech and math	17.44	33.95
YSR externalizing	52.12	9.63
YSR internalizing	52.92	10.26

SAVE = Screen for Adolescent Violence Exposure; CTQ = Childhood Trauma Questionnaire; YSR = Youth Self Report; RSA = respiratory sinus arrhythmia; DHEA-S = dehydroepiandrosterone sulfate; PEP = Pre-ejection period.

associations were observed between poverty and baseline SNS activity, or between interpersonal violence and any physiological measure.

Next, we examined associations between adversity exposure and physiological reactivity. Table 3 displays coefficients, standard errors, and significance values for hierarchical linear regression models predicting physiological reactivity (RSA, PEP, and cortisol:DHEA-S) from poverty and interpersonal violence. Neither violence nor poverty predicted PNS reactivity to speech or math. Exposure to violence was associated with blunted SNS reactivity to the speech and math portions of the TSST. Findings did not change when adjusting for poverty. In contrast, poverty was unassociated with SNS reactivity, with or without adjusting for violence. Finally, interpersonal violence was associated with blunted HPA-axis response to the TSST, even when accounting for poverty. In contrast, poverty was unrelated to HPA-axis reactivity, even when accounting for interpersonal violence.

Physiological Reactivity and Psychopathology

Next, we tested the hypothesis that physiological reactivity would be associated with symptoms of psychopathology. Symptoms of externalizing psychopathology were associated with blunted physiological reactivity. Blunted SNS and PNS reactivity to math (SNS: b = .15, p = .017; PNS: b = 1.14, p = .050) and decreased HPA-axis activation after the TSST (b = −2.55, p = .008) were associated with greater externalizing symptoms. Neither SNS, PNS, nor HPA-axis reactivity were associated with internalizing symptoms.

Mediation Analysis

Finally, we ran separate mediation models to test whether physiological reactivity to the TSST mediated the association

TABLE 2. Bivariate Correlations Among Physiology, Childhood Adversity, Psychopathology, and Demographic Variables (N = 167)

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	—												
2. Female	−.12	—											
3. Poverty	−.01	−.06	—										
4. Interpersonal violence	.22**	−.05	.21**	—									
5. PEP (baseline)	.29**	−.09	.10	.07	—								
6. PEP (speech)	.18*	−.19*	.12	.16*	.68**	—							
7. PEP (math)	.18*	−.10	.13	.18*	.74**	.90**	—						
8. RSA (baseline)	−.10	.08	.15	.01	−.02	.01	−.04	—					
9. RSA (speech)	−.02	−.15	.21*	.16*	.20*	.46**	.43**	.16*	—				
10. RSA (math)	−.05	.01	.13	.14	.10	.30**	.33**	.37**	.67**	—			
11. LogCortisol:DHEA (baseline)	.00	.12	.20*	.10	−.07	−.08	−.08	.13	−.04	.06	—		
12. LogCortisol:DHEA (after speech)	−.09	.13	.20*	−.02	−.05	−.15	−.14	.17*	−.07	.04	.84**	—	
13. YSR externalizing	.15	.07	.21**	.48**	.03	.09	.13	.07	.15	.18*	−.01	−.13	—
14. YSR internalizing	.19*	.04	.10	.44**	−.07	−.00	−.01	−.04	.11	.02	−.09	−.15	.54**

YSR = Youth Self-Report; PEP = pre-ejection period; RSA = respiratory sinus arrhythmia

*p < .05; **p < .01.

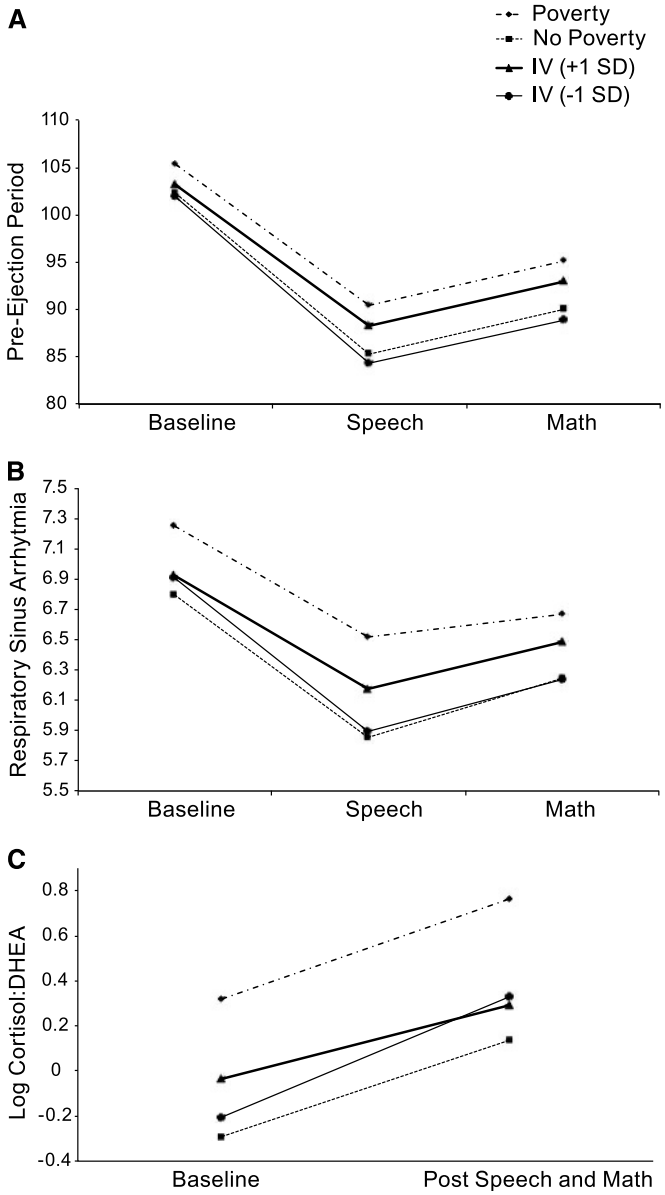

FIGURE 1. Physiological reactivity to the TSST, by exposure to poverty and interpersonal violence. Panels display SNS (top), PNS (middle), and HPA-axis (bottom) reactivity. Interpersonal violence (IV) is shown at +1 and −1 standard deviations from the mean. Data are unadjusted for covariates.

of violence exposure with internalizing and externalizing symptoms. Adjusting for poverty, a significant indirect effect of violence exposure through HPA-axis reactivity, was observed (N = 156; 95% confidence interval, .03–.45) (Fig. 2). We found no significant indirect effect of violence through SNS reactivity to speech or to math.

Sensitivity Analysis

We conducted sensitivity analyses to determine whether our dichotomous operationalization of poverty explained our findings. The pattern of findings was identical when using income-to-needs ratio as a continuous measure.

DISCUSSION

The present study provides evidence for distinct effects of deprivation and threat on ANS and HPA-axis development. Disturbances in autonomic and neuroendocrine system function are a putative mechanism underlying the association between CA and psychopathology (8,67). However, findings from previous studies have been highly mixed, suggesting the need to disentangle the relative impacts of different forms of CA.

We extend previous research in a number of ways. First, we tested a novel theoretical model that differentiates between experiences of deprivation and threat in shaping neurobiological development (26,27). Consistent with this

TABLE 3. Summary of Hierarchical Regression Analysis for Effects of Poverty and Interpersonal Violence on Physiological Reactivity (N = 167)

	Speech			Math		
Physiological Measure	b	SE	*p*	b	S.E	*p*
RSA						
IV	.09	.07	.19	.09	.07	.19
Poverty	.45	.25	.071	.15	.25	.55
IV (controlling for poverty)	.07	.07	.32	.08	.07	.22
Poverty (controlling for IV)	.40	.25	.11	.09	.25	.70
PEP						
IV	1.51	.72	.035	1.65	.61	.007
Poverty	2.48	2.64	.35	2.47	2.30	.28
IV (controlling for poverty)	1.44	.73	.050	1.59	.63	.012
Poverty (controlling for IV)	1.33	2.67	.62	1.20	2.31	.60
	After Speech and Math					
	b	SE	*p*			
Cortisol:DHEA-S						
IV	−.08	.04	.033			
Poverty	.09	.14	.50			
IV (controlling for poverty)	−.09	.04	.021			
Poverty (controlling for IV)	.15	.14	.28			

RSA = Respiratory sinus arrhythmia; PEP = pre-ejection period; DHEA-S = dehydroepiandrosterone sulfate; IV = interpersonal violence. Analyses control for age, sex, baseline reactivity and respiration rate (for models with RSA).

Analyses control for age, sex, baseline reactivity, and respiration rate (for models with RSA).

model, our data support the hypothesis that whereas both forms of CA, reflected in poverty and interpersonal violence exposure, are associated with higher levels of psychopathology, only threat is associated with differences in physiological reactivity. Specifically, we found that threat was associated with blunted SNS and cortisol reactivity to the TSST, and that HPA-axis reactivity mediated the association between threat and externalizing psychopathology. In contrast, we found no association between threat and PNS reactivity, or any associations between physiological reactivity and internalizing symptoms. These findings are consistent with previous studies reporting blunted physiological reactivity to stress in individuals with exposure to interpersonal violence, such as maltreatment (15,17,23) and with those reporting blunted physiological reactivity in children with externalizing disorders (53,54). Blunted cortisol reactivity could reflect down-regulation of corticotropin-releasing hormone receptors in the pituitary gland after iterative exposure to interpersonal violence. In turn, this pattern of reduced reactivity to environmental stressors may contribute to externalizing pathology by chronically reducing arousal levels and increasing sensation seeking (68). Notably, despite finding differences in baseline HPA-axis activity among poverty-exposed adolescents, there was no association between poverty and physiological reactivity, with or without adjusting for interpersonal violence. This departs from a number of prior studies of poverty-exposed youth (11,69). These findings suggest that studies examining

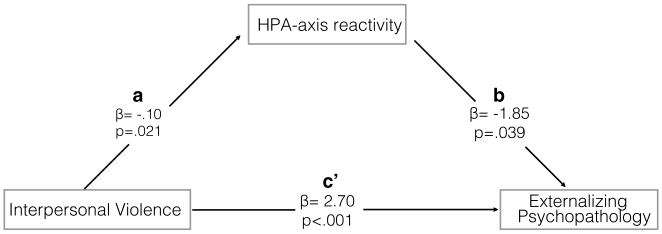

FIGURE 2. Hypothalamic-pituitary-adrenal axis reactivity mediates the association between interpersonal violence exposure and externalizing psychopathology. The significance of the indirect effect was tested using a bootstrapping approach, and analyses adjust for age, sex, poverty, and HPA-axis activity at baseline. c' = direct effect.

poverty and physiological reactivity to stress should assess and control for exposure to violence, which may be a critical confounder.

Second, our findings show that interpersonal violence was associated with blunted SNS reactivity to the TSST. To date, surprisingly few prior studies have explored the impact of adversity exposure on ANS reactivity, and these studies have often used nonspecific measures such as heart rate (15,70). Our use of pre-ejection period is advantageous, as it represents a measure of pure sympathetic response. The importance of differentiating between contributions of the SNS and PNS is underscored by our finding that only SNS indicators are associated with exposure to threat. In contrast, in previous studies, we (and others) have found that PNS reactivity to psychosocial stress functions as a *moderator*, such that risk of internalizing psychopathology after exposure to CAs varies as a function of PNS activity (71,72). Taken together, these results suggest that measures of ANS activity, particularly of the SNS, may be used as a clinically useful index of stress sensitivity after exposure to violence in childhood alongside commonly used HPA-axis measures such as cortisol.

The findings from this study should be viewed in light of several limitations. First, our data are cross-sectional, precluding us from determining the directional and transactional pathways linking CA exposure, physiological reactivity, and externalizing psychopathology. Our mediation analyses assume a temporal ordering of relationships, but it is possible that externalizing symptoms precede rather than follow from blunted physiological reactivity to stress. It is plausible that youths with externalizing problems may put themselves at increased risk for exposure to interpersonal violence (e.g., by engaging in community violence). Future prospective studies are needed to explore bidirectional associations between these variables. Second, our assessment of psychopathology used a self-report questionnaire. Replication of these findings using a structured clinical interview is therefore warranted. Third, our model focuses on only two aspects of early experience, and there are likely to be numerous others. For example, other characteristics of adversity, including the developmental timing and chronicity of exposure, have been conceptualized as important components of CA that explain differences in neuroendocrine activity and psychopathology in later life (73–75). Further studies are needed to examine the impact of additional dimensions of adversity on neurobiological development and mental health. Fourth, we did not collect information on females' use of oral contraceptives, which may have affected analyses involving HPA-axis reactivity. However, given the age of the sample, we find this to be unlikely. Finally, our study design did not allow us to examine moderators of the association between childhood adversity and psychopathology. An enhanced understanding of factors that may buffer individuals from early adversity is another important goal for future research.

CONCLUSIONS

We provide evidence for differential influences of threat and deprivation on physiological reactivity to stress. Although both deprivation and threat exposure were associated with greater levels of externalizing symptoms, only threat exposure was associated with differences in physiological reactivity. Blunted physiological reactivity, in turn, mediated only the association of threat with externalizing problems. These findings provide preliminary support for the deprivation/threat model as a useful theoretical framework through which to understand the association of childhood adversity with neurobiological development. Moreover, these findings highlight the importance of distinguishing between different forms of adversity. Such an approach may eventually yield information that can be used to targeting intervention approaches based on disorder etiology, in addition to symptomatology.

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