Harsh Parenting and Youth Systemic Inflammation:
Modulation by the Autonomic Nervous System

Assaf Oshri, Ph.D.¹²³, Erinn Bernstein Duprey, Ed.M.¹³, Sihong Liu, M.S.¹³, Katherine B.
Ehrlich, Ph.D.²⁴.

The University of Georgia, Department of Human Development and Family Science¹

The University of Georgia, Department of Psychology²

The Youth Development Institute³

The Center for Family Research⁴

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Correspondence concerning this article should be addressed to Assaf Oshri, The Youth Development Institute, Department of Human Development and Family Science, Athens, GA 30602. Contact: oshri@uga.edu

Abstract

Objective: The present study aimed to test the role of the autonomic nervous system (ANS) in modulating the impact of family stress, induced by harsh parenting, on youths' inflammation. First, we examined the direct effect of severity of adverse parenting behaviors on two serum biomarkers of systemic inflammation (C-reactive protein and interleukin-6) among youth. Second, we tested the moderating role of ANS reactivity in response to laboratory-induced stress in the association between harsh parenting and inflammation among these youth. **Methods:** The sample included 101 low-income children (75.2% African-American) between 9 and 12 years of age ($M_{age}=10.9$; $SD_{age}=1.2$) who participated in a conflict task with their primary caregiver in a laboratory setting. Heart rate variability reactivity (HRV-R), skin conductance level reactivity (SCL-R), and pre-ejection period reactivity (PEPr-R) were used to index parasympathetic and sympathetic nervous system reactivity. Markers of low-grade inflammation (C-reactive protein and interleukin-6) were obtained from serum. **Results:** After adjusting for confounding variables, ANS activity moderated the associations between family stress and systemic inflammation. Specifically, elevated HRV-R buffered the effect of family stress on youths' inflammation, whereas elevated PEPr-R and SCL-R exacerbated the effect. **Conclusion:** These findings show that self-regulatory capacity and threat sensitivity, as indicated by ANS function, may have an impact on the associations between family stress and systemic inflammation.

Keywords: Early life stress, inflammation, autonomic nervous system, biological sensitivity

Acronyms: ANS = autonomic nervous system; HRV-R = heart rate variability reactivity; PEPr-R = pre-ejection period reactivity; SCL-R = skin conductance level reactivity; IL-6 =

interleukin 6; CRP = C-reactive protein; SNS = sympathetic nervous system; PNS =
parasympathetic nervous system

Harsh Parenting and Youth Systemic Inflammation: Modulation by the Autonomic Nervous System

Children raised by parents who use harsh parenting tactics experience enduring stress that can affect a wide range of health outcomes across the lifespan (Repetti, Robles, & Reynolds, 2011). A growing body of research suggests that family stress is biologically embedded via aggressive inflammatory responses that compromise the immune system and lead to poor health outcomes (Nusslock & Miller, 2016; Slopen, Kubzansky, McLaughlin, & Koenen, 2013). Indeed, being reared in an adverse family climate is linked to low-grade inflammation that is evidenced as early as childhood and adolescence (Slopen et al., 2013). However, not all youth who experience harsh parenting develop elevated systemic inflammatory risk. According to biological sensitivity to context models (Boyce & Ellis, 2005; Ellis & Boyce, 2011), individual differences in patterns of the autonomic nervous system (ANS) functioning can moderate the risk for inflammatory response intensity, as part of an individual's physiological adaptation to early life stress.

Theoretical models on the physiological impact of stress on inflammatory responses converge to suggest that the ANS and the immune system are not fully independent from each other (Pereira & Leite, 2016). Consistent with these models of stress physiology and biological sensitivity to context (Ellis & Boyce, 2008; Obradović, Bush, Stamperdahl, Adler, & Boyce, 2010), we conceptualize youths' ANS response sensitivity to environmental stimuli as a neurobiological context and suggest that variability in ANS response sensitivity may exacerbate or attenuate youths' inflammation response when exposed to harsh parenting. Despite the growing evidence and theory connecting stressful family experiences with low-grade inflammation (Nusslock & Miller, 2016; Repetti et al., 2011), scarce empirical attention has been

given to the role of the ANS in this connection among youth. The present study seeks to fill gaps in knowledge on the moderating role of ANS stress response reactivity for the link between harsh rearing environments and low-grade inflammation. This research focuses on an ethnically diverse and low-income sample, an at-risk yet understudied population. Among ethnic minority samples, more firm and authoritative parenting has been found to have unique protective effects (Brody, Dorsey, Forehand, & Armistead, 2002), yet less is known on the effect of ANS in the connection between parenting and inflammation risk among these youth (Gatzke-Kopp, 2016).

Family Stress and Low-Grade Inflammation Risk

Family stress is significantly linked to heightened inflammation among adults (Beach, Lei, Brody, Dogan, & Philibert, 2015; Danese et al., 2008; Miller, Rohleder, & Cole, 2009) and youth (Miller & Chen, 2010; Slopen et al., 2013). For example, Miller and Chen (2010) showed that adolescent girls who were raised in risky families evinced pro-inflammatory (IL-6) responses to both an in-vitro challenge that used bacterial products and a real-life psychological stressor. Similarly, in a large prospective study, adverse life events such as harsh parenting were associated with elevations in IL-6 and C-reactive protein (CRP) during childhood and adolescence (Slopen et al., 2013). Emerging research has also identified protective factors for the impact of early adversity on inflammation. In a longitudinal study with families of youths aged 11-13, Beach et al. (2015) found that protective parenting buffered the effect of early life stress on systemic pro-inflammatory processes. Similarly, Nelson et al. (2017) reported exposure to positive parenting buffered the association between resting SNS activity and elevated salivary CRP among youth. Nonetheless, despite interest in the mechanisms linking parenting and elevated inflammation in youth, less research has evaluated psychophysiological

risk and protective factors that may affect the impact of family stress resulting from harsh parenting on impoverished minority youth inflammation risk.

The Autonomic Nervous System and Self-Regulation

In response to stressful family environments, the child's stress system is partially activated via the ANS, which results in physiological adaptations that facilitate coping with the threat (Obradović et al., 2010). Such neurobiological adaptations to environmental stimuli are described by biological sensitivity to context models (Ellis & Boyce, 2008). Accordingly, response sensitivity to psychosocial stressors is modulated by the ANS, potentially enabling more effective coping with stress. This hypothesis is consistent with psychobiological models suggesting ANS biomarkers serve as top-down self-regulation indices (Holzman & Bridgett, 2017) that can modulate youths' response to social threats and the associated stress (Porges, 2007).

Functionally, the ANS is divided into two major branches, the sympathetic and parasympathetic systems. The sympathetic nervous system (SNS) is responsible for energy mobilization, and the parasympathetic nervous system (PNS) facilitates energy conservation and restorative functions. The SNS is an important component in buffering the immune response through its active role in maintaining homeostatic ANS functioning (Thayer & Sternberg, 2006). Skin conductance (SCL) reactivity and pre-ejection period (PEP) reactivity are two measures that are often utilized to measure the activity of the SNS. SCL reactivity refers to galvanic skin response or electrodermal reactivity and reflects the arousal of the SNS via the activity of sweat glands. An abundance of psychophysiological and fMRI research suggests that SCL-R is controlled by SNS activity (Critchley, Elliott, Mathias, & Dolan, 2000). Individuals with heightened SCL-R may experience high anxiety or fearfulness and exhibit inhibited behavior

when faced with perceived threat (Beauchaine, 2001; El-Sheikh, Erath, Buckhalt, Granger, & Mize, 2008; Fowles, Kochanska, & Murray, 2000).

An additional index of SNS functioning is the pre-ejection period (PEP), also termed ventricular ejection time. The PEP, assessed using impedance cardiography (Cacioppo, Uchino, & Berntson, 1994), refers to the passage of time between when the heart fills and is ejected with blood out of the heart. PEP is an established measure of SNS activity (Berntson et al., 1994; Quigley & Stifter, 2006). Psychophysiological research suggests that lower PEP indicates higher SNS activity and heart rate acceleration (Quigley & Stifter, 2006). A growing body of research with children suggests that PEP is a precise index of SNS functioning that reflects trait impulsivity or approach motivation under conditions of reward (Brenner, Beauchaine, & Sylvers, 2005; Richter & Gendolla, 2009).

The ANS regulatory function towards homeostasis is achieved through the complementary and counterbalancing activity of the PNS (Buijs, 2013). The ability of the PNS to rapidly modulate cardiac activity allows for more effective engagement and flexibility in response to environmental demands with physiological and emotional arousal (Porges, 2007). For example, heart rate variability (HRV) is a physiological parameter that has been shown to reflect self-regulatory capacities via its activation by the ANS (Appelhans & Luecken, 2006; Thayer & Siegle, 2002). High-frequency HRV is derived by measuring the normative variation in heart rate between expirations and inspirations. This variability in heart rate is induced by the activity of the vagus nerve, the tenth cranial nerve, which is a major component of the parasympathetic branch of the ANS. Consequently, vagal activity (i.e., *vagal tone*) has been quantified by measuring the high amplitude of HRV (Porges, Doussard-Roosevelt, & Maiti,

1994). Growing research provides evidence that the ANS directly innervates (Kemeny & Schedlowski, 2007) and regulates (Nance & Sanders, 2007) the immune system.

The Autonomic Nervous System and Systemic Inflammation Risk

The SNS is associated with the upregulation of inflammation, and the PNS is associated with decreasing inflammation (Fagundes & Way, 2014; Thayer & Sternberg, 2006). These associations have recently been supported by a meta-analysis (Williams et al., 2019). Indeed, extant research on biological sensitivity to context suggests that the functioning of both the PNS and SNS may increase risk or provide protection in the context of family conflict (Del Giudice, Hinnant, Ellis, & El-Sheikh, 2012; El-Sheikh & Erath, 2011; Hinnant, Erath, & El-Sheikh, 2015). ANS reactivity, in response to stress, may affect children's sensitivity to the experiences of family conflict (Del Giudice et al., 2012). Thus, based on biological sensitivity to context theory and research, the ANS system may serve as a biological factor that modulates the link between early life stress and systemic inflammation. Yet, there are scarce empirical studies to test this hypothesis.

The Current Study

Despite theoretical advances on the association between family stress and health risk outcomes (Juster et al., 2011; Repetti et al., 2011), less is known about the role of the ANS as a moderator of the link between family stress and inflammation. The first aim of the present study was to examine the association between family stress and elevation in low-grade inflammation. The second aim was to test whether youths' stress response reactivity, measured through ANS functioning during a conflict task with caregivers, moderates the association between family stress and chronic inflammation. We used three key physiological indices for ANS functioning that have been systematically studied in the context of parenting and family context (El-Sheikh

& Erath, 2011): One from the PNS branch, which was heart rate variability reactivity (HRV-R), and two from the SNS branch, including skin conductance level reactivity (SCL-R) and cardiac pre-ejection period reactivity (calculated using R onset; PEPr-R). Increased SNS activity and decreased vagal activity are linked to immune risk (Cooper et al., 2015; Irwin & Cole, 2011; Marsland et al., 2007; Sajadieh et al., 2004). Similarly, studies show that, while the SNS has pro-inflammatory effects, the PNS has a protective anti-inflammatory effect (Fagundes & Way, 2014; Thayer & Sternberg, 2006). We hypothesized that family stress would predict increased elevations in CRP and IL-6 after controlling for confounding variables. We also hypothesized that HRV-R, SCL-R, and PEPr-R would moderate the link between family stress and low-grade inflammation. More specifically, PEPr-R and SCL-R (SNS indicators) were expected to intensify the link between family stress and inflammation, whereas HRV-R (a PNS indicator) was expected to attenuate this link.

Materials and Methods

Sample

Youths aged 9 through 12 years ($M_{age} = 10.27$, $SD_{age} = 1.19$) and their primary caregivers ($N = 101$) were recruited for a pilot study from a non-metropolitan region of the Southeastern United States. Inclusion criteria included being below 200% of the federal poverty level in the year 2017 (i.e., an annual income of \$48,600 for a family of four) and proficiency in English. Participants were screened out if they had a history of a heart condition, if the parent was pregnant, and if the youth had type II diabetes, significant developmental disabilities, or a high fever. The full sample was mostly non-White (75.2% African-American or Black, 10.9% White, 8.9% Latino, 1.0% Native American, and 4.0% other). There was an even distribution of gender among the youth (52.0% female). Primary caregivers were aged from 24 to 51 years old ($M_{age} =$

35.51, $SD_{age} = 6.51$), and they were mostly mothers (90.1%). Additionally, approximately 8.8% ($n = 8$) and 16.5% ($n = 16$) of families had an open or closed case with child protective services, respectively.

Procedures

All study procedures were approved by the Institutional Review Board at the University of Georgia. Participants were recruited via online and in-person advertisements and through paid recruiters who were active members of the community. Before participating in any study tasks, participants provided their informed consent and assent. All aspects of the study took place at a university clinical research unit affiliated with the University of Georgia. Upon arrival at the research unit, children's temperatures were taken by a pediatric nurse as part of the screening procedure. Children with a fever ($>37^{\circ}\text{C}$) were excluded from the study. Trained research staff and licensed pediatric research nurses implemented all study procedures.

After obtaining informed consent and assent for the study, registered nurses collected blood via venipuncture into a 5ml serum separator tube, which was allowed to clot for 30 minutes at room temperature. Serum was then centrifuged at 3000RPM for 15 minutes. Serum aliquots of 300ul were put into two 1.5ml microtubes and frozen at -80°C for subsequent analysis of IL-6. Remaining serum was sent to a local hospital for analysis of CRP. To obtain autonomic nervous system parameters, a mobile electrocardiogram was utilized with seven attached dermal ECG electrodes and two dermal electrodes for skin conductance. Pediatric ECG electrodes were placed on both sides of the child's clavicle and lower rib cage, on the sternum, and on the upper and lower spine. Two galvanic skin conductance electrodes were placed on the child's non-dominant hand, and on the thenar and hypothenar eminence. To obtain resting measures of ANS system activity, participants were instructed to remain in a seated position and

relax while they listened to a five-minute video of nature sounds. These procedures were established based on standard recommendations for obtaining HRV (Malik et al., 1996).

After baseline, youths and their parents remained seated and completed a videotaped conflict task in which they were instructed to discuss common topics of disagreement (e.g., homework). The measurement of the parent-adolescent conflict task was modeled after widely used semi-structured observational tasks (e.g. Kobak, Cole, Ferenz-Gillies, Fleming, & Gamble, 1993). Topics were placed on index cards and given to the child by the research staff. The research staff instructed dyads to choose and discuss the three topics that they had the most disagreement on. Dyads were given a total of eight minutes to choose the three topics and discuss their disagreements about them. Researchers advised parents and youths to try for progress towards consensus on each topic. If the parent and youth completed discussing their three chosen topics early, they were instructed to choose and discuss additional topics. Researchers left the room for the duration of the discussion task. Conflict tasks between parents and youths have been shown to elicit stress among youths (Cui et al., 2015; Ehrlich, Dykas, & Cassidy, 2012). This is also confirmed in a recent meta-analysis that included 13 studies consisting of 787 participants who took part in social interactions while measuring HRV (Shahrestani, Stewart, Quintana, Hickie, & Guastella, 2015). After completing the conflict task and an additional five-minute relaxation period, the mobile electrocardiogram was disconnected. Youths and caregivers then completed a series of questionnaires using a handheld tablet or laptop.

Measures

Inflammatory parameters. Systemic inflammation was quantified via serum levels of IL-6 and CRP. CRP was measured in singlet using a high-sensitivity Near-Infrared Particle

Immunoassay rate methodology. Using Luminex technology, IL-6 was measured in triplicate with a bead-based multiplex assay (HCYTOMAG-60K, EMD Millipore, Billerica MA). The CRP had a minimum detection threshold of .20 mg/L. The IL-6 had a minimum detection threshold of 3.35 pg/ml with an intra-assay coefficient of variation of 2.89%. CRP and IL-6 were both modeled as continuous outcomes. For both CRP and IL-6, values below the minimum detection threshold were coded as the threshold values (i.e., .20 mg/L for CRP, $n = 23$; 3.35 pg/ml for IL-6, $n = 32$). A total of six CRP values that were above 10 were recoded as missing, as scores over 10 generally indicate that the child had a recent illness. We then investigated outliers for CRP and IL-6. Three CRP scores and two IL-6 scores were found to be more than three standard deviations above the mean. We winsorized these outliers by recoding their values to equal three standard deviations above the mean. After recoding CRP and IL-6 values, these variables were log-transformed due to positive skewness.

Sympathetic nervous system parameters. Sympathetic nervous system activity was collected using a mobile impedance cardiograph (MindWare Technologies, Ltd., Gahanna, OH). Four pediatric spot electrodes were utilized to obtain electrical impedance. Two electrodes were placed on the youth's upper and lower back, and two electrodes were placed on the youth's front at their clavicle and sternum. Impedance cardiography analysis was performed to isolate the sympathetic influence on the heart. Specifically, PEPr was measured, which indicates the time interval between the initial electrical stimulation of the heart (onset of the R peak) and the opening of the aortic valve (B point of the dZ/dT wave; Lozano et al., 2007). Using the MindWare IMP 3.1.4 Software module, impedance data were ensemble-averaged in 30-second epochs in combination with R waves that were obtained from the electrocardiogram. Trained research assistants used video recordings to cross-inspect and correct the abnormal R-R intervals,

such as severe fluctuations, inadvertent cardiac fluctuations, and ectopic beats due to physical movement or breathing. Mean values of PEPr across the 30-second epochs were calculated for the baseline and stress conflict task, respectively.

To measure PEPr-R, a residualized change score (Cacioppo et al., 1994) was created using the mean level of PEPr during the rest period ($M = 77.42$, $SD = 24.75$) and during the stress task, $M = 79.36$, $SD_{PEPr} = 22.43$, $r(PEPr_{Stress}, PEPr_{Baseline}) = .78$. This type of calculation allowed us to adjust for the variance in PEPr baseline (Berntson et al., 1997). Lower PEPr residualized change scores (i.e., $\Delta PEPr$) indicate a decrease from baseline to the stress task and are indicative of high levels of PEPr stress reactivity.

$$\Delta PEPr = \frac{PEPr_{Stress} - PEPr_{Baseline}}{SD(PEPr_{Baseline}) \times \sqrt{1 - r(PEPr_{Stress}, PEPr_{Baseline})}}$$

SCL activity was collected using two electrodermal electrodes placed on the participants' non-dominant hand. Physiological data were analyzed using the Mindware EDA 3.1.4 Software module, and SCL data were ensemble-averaged in 30-second epochs. Then, the mean values of SCL across the 30-second epochs during baseline and stress conflict task were calculated respectively. To measure SCL-R, a residualized change score (Cacioppo, Uchino, & Berntson, 1994) was created using the mean level of SC during the rest period ($M = 6.59$, $SD = 5.20$) and during the stress task, $M = 12.09$, $SD = 6.54$, $r(SCL_{Stress}, SCL_{Baseline}) = .88$. This calculation allowed us to adjust for the variance in SCL baseline (Berntson et al., 1997). Higher SCL residualized change scores (i.e., ΔSCL) indicate a decrease from baseline to the stress task and are indicative of high levels of SCL stress reactivity.

$$\Delta SCL = \frac{SCL_{Stress} - SCL_{Baseline}}{SD(SCL_{Baseline}) \times \sqrt{1 - r(SCL_{Stress}, SCL_{Baseline})}}$$

Parasympathetic nervous system. All procedures were in accordance with current standards for measuring HRV in psychophysiological research (Berntson et al., 1997). Three spot electrodes were utilized to obtain HRV and were placed on either side of the lower rib cage and on the right clavicle. HRV was measured using the BioNex system from MindWare Technologies (Gahanna, OH). The MindWare HRV 3.1.4 Software module was utilized to digitize heart rate data, and HRV data were ensemble-averaged in 30-second epochs. The high-frequency bandpass was set at .12 to .40 with a sample rate set of 1000 Hz. The high-frequency components of HRV were obtained via power spectrum analysis (Akselrod et al., 1981) in order to isolate the influence of parasympathetic activity on HRV-R (Akselrod et al., 1981; Appelhans & Luecken, 2006). Baseline cardiography and respiration were calculated using spectral analysis of thoracic impedance to control for noise in data collection (Ernst, Litvack, Lozano, Cacioppo, & Berntson, 1999). Trained researchers also inspected and removed severe inadvertent cardiac fluctuations that were caused by participants' physical movement or breath. An interpolation algorithm was utilized to convert inter-beat intervals into 120s segments, and a MAD/MED algorithm was utilized to detect physically improbable IBIs. The minimum and maximum heart rate were set at 40/minute and 200/minute, respectively. Mean values of HRV across the 30-second epochs were calculated during baseline and stress conflict tasks. To calculate HRV-R, a residualized difference score (Cacioppo et al., 1994) was calculated using the youth's mean HRV during the rest period ($M = 6.95$, $SD = 1.19$) and the stress task ($M = 6.79$, $SD = 1.04$, r ($HRV_{\text{Stress}}, HRV_{\text{Baseline}}$) = .85). This type of calculation allowed us to adjust for the variance in baseline HRV (Berntson et al., 1997). Lower HRV-R residualized change scores (i.e., lower ΔHRV) indicate a decrease from baseline to the stress task and are indicative of high levels of HRV-R and more self-regulation.

$$\Delta HRV = \frac{HRV_{Stress} - HRV_{Baseline}}{SD(HRV_{Baseline}) \times \sqrt{1 - r(HRV_{Stress}, HRV_{Baseline})}}$$

Family stress. The Parent-Child Conflict Tactics Scale (CTS-PC; Straus, Hamby, Finkelhor, Moore, & Runyan, 1998) was utilized to measure harsh parenting. Parents responded to items regarding actions that they have taken towards their children in the past year. Five subscales were utilized which included corporal punishment, psychological aggression, weekly discipline, nonviolent discipline, and neglect. The corporal punishment subscale was calculated with a sum score from six items ($\alpha = .83$). Example items include “*shook him/her (the child)*” and “*spanked him/her on the bottom with bare hand.*” The psychological aggression subscale was calculated with a sum score from five items ($\alpha = .72$). Example items include “*shouted, yelled, or screamed at him/her*” and “*swore or cursed at him/her.*” The nonviolent discipline subscale was obtained by a sum score of four items ($\alpha = .79$), and the example items include “*Put him/her in "time out" or sent to his/her room*”. The weekly discipline subscale was calculated with a sum score from four items ($\alpha = .76$). An example item includes “*shouted, yelled, or screamed at your child.*” The neglect subscale was calculated with a sum score from four items ($\alpha = .70$). An example item includes “*had to leave your child home alone, even when you thought some other adult should be with him/her.*”

Control variables. Parents reported the youth’s age. The licensed pediatric nurse measured youth’s waist circumference and took youth’s systolic and diastolic blood pressure three times. The average values of the three blood pressure assessments were used in the analyses. Youth’s resting heart rate was obtained during the baseline period.

Analysis

All hypotheses were tested using a structural equation modeling framework in Mplus version 7.4 (Muthén & Muthén, 2010). Models were determined to have a good fit if they

exhibited CFI values over 0.95 and SRMR values below 0.08 (Hu & Bentler, 1999). The missing data rate ranged from 0.0% to 34.7% with an average of 14% across all variables. Missing data were mostly found in the inflammatory parameters (i.e., CRP and IL-6). Specifically, there were 31.7% ($n = 32$) youths who rejected the blood draw with 3.0% ($n = 3$) data missing on both CRP and IL-6 due to administrative and analytical errors. For CRP, as mentioned earlier, there were 5.9% ($n = 6$) scores recoded as missing because the raw CRP levels indicated the child had a recent illness. Additionally, there were 7.9% ($n = 8$) data missing on ANS physiological stress reactivity due to participants' excessive movement and administration errors. Little's Missing Completely at Random (MCAR) test suggested that missing data patterns met the MCAR assumption ($\chi^2(127) = 131.20, p = .38$). Therefore, the full-information maximum likelihood was used to estimate the missing data (Rubin & Little, 2002). A confirmatory factor analysis was modeled to test the factor structure of family stress by using the various subscales of the CTS. Then, a series of structural equation models were tested to investigate the moderating roles of Δ HRV, Δ SCL, and Δ PEPr in the association between harsh parenting and two inflammatory markers (IL-6 and CRP). Interaction terms were created between the latent harsh parenting variable and the moderator variables and added to the models in order to test the moderating effects. Moderation was assumed if these interaction terms were significantly associated with the outcome variable. In each model, we employed the Bonferroni correction to correct for multiple comparisons (i.e., CRP vs. IL-6 as outcome variables). In order to interpret moderation and give a full elucidation of the interaction effects, significant interactions were probed using the Johnson-Neyman technique (Johnson & Neyman, 1936) and a method adopted from the simple slope analysis (Aiken, West, & Reno, 1991; Dawson, 2014) by Kim and Kochanska (2012). The Johnson-Neyman technique presents the effect of family stress

on youths' inflammatory responses and its 95% confidence interval contingent on different values of the moderator (i.e., un-centered Δ HRV, Δ SCL, and Δ PEPr, respectively). The adapted simple slope method presents the slope of the main effects contingent on different values of moderators and shows the regions of significance.

Results

Descriptive Statistics and Measurement Model

Table 1 presents the descriptive statistics and correlations of study variables. Among the 101 youth, there were 54.8% who showed decreased HRV (i.e. PNS withdrawal), 98.9% who presented increased SCL (i.e. SNS activation), and 41.9% who exhibited decreased PEPr (i.e. SNS activation) from baseline to the stress task. A confirmatory factor analysis was conducted to test the factor structure of harsh parenting. Nonviolent discipline was removed from the model due to a low factor loading coefficient ($< .30$; Brown, 2015). Subsequently, a one-factor latent construct of family stress consisting of four indicators (i.e., corporal punishment, psychological aggression, weekly discipline, and neglect) was supported by the data. Factor loadings were moderate to high and significant for corporal punishment ($\lambda = .71$, $SE = .08$, $R^2 = .60$, 95% CI of λ [.56, .86], $p < .001$), psychological aggression ($\lambda = .64$, $SE = .09$, $R^2 = .50$, 95% CI of λ [.46, .81], $p < .001$), weekly discipline ($\lambda = .66$, $SE = .08$, $R^2 = .66$, 95% CI of λ [.51, .81], $p < .001$), and neglect ($\lambda = .61$, $SE = .09$, $R^2 = .63$, 95% CI of λ [.42, .79], $p < .001$). The resulting model fit was excellent: $\chi^2 (1) = .41$ ($p = .52$), CFI = 1.00, SRMR = .01.

Structural Equation Models

A structural equation model was constructed to test the direct association between a latent variable for family stress with CRP and IL-6. The model exhibited excellent fit: $\chi^2 (18) = 18.80$ ($p = .40$), CFI = .99, SRMR = .09. Family stress was not significantly associated with IL-6 ($\beta =$

.18, 95% *CI* [-.07, .43], $p = .17$), nor with CRP ($\beta = -.11$, 95% *CI* [-.32, .10], $p = .32$). As expected, IL-6 was significantly correlated with CRP ($\beta = .39$, 95% *CI* [.18, .56], $p < .001$).

Structural equation models were then constructed to test the moderating roles of HRV-R, SCL-R, and PEPr-R on the associations between family stress and inflammation after controlling for youth age, waist circumference, resting heart rate, and blood pressure. Latent interaction factors reflecting the product of the latent variable of family stress and each of the physiological indexes of ANS (i.e., Δ HRV, Δ SCL, and Δ PEPr) were added to the models (Klein & Moosbrugger, 2000; Marsh, Wen, & Hau, 2004). All models presented adequate fit indices (See Table 2). The left columns of Table 2 and panel (A) of Figure 2 present the moderating effect of HRV-R on the effects of family stress on inflammatory indices. Results indicated that the latent interaction factor of harsh parenting and Δ HRV was significantly associated with higher levels of IL-6 ($\beta = .37$, 95% *CI* [.03, .16], $p = .006$) but was not associated with CRP. Figure 3 presents the interpretation of this moderating effect. For youths with high HRV-R (i.e., more PNS withdrawal; Δ HRV ≤ 1.15 ; 89.2% of participants), the association between family stress and IL-6 was non-significant. For youths with low HRV-R (i.e., less PNS withdrawal; Δ HRV > 1.15 ; 10.8% of participants), this association was positive and significant. In other words, higher levels of PNS withdrawal during the stress task indicated by HRV-R plays a protective role in youths' inflammatory responses under adverse rearing environments.

The middle columns of Table 2 and Panel (B) of Figure 2 present the moderating effect of SCL-R on the effect of family stress on inflammatory indices. Results indicated that the latent interaction factor of family stress and Δ SCL was significantly associated with higher levels of IL-6 ($\beta = .26$, 95% *CI* [.04, .65], $p = .025$), but it was not significantly associated with CRP. Figure 4 presents the interpretation of this moderating effect. For youths with high SCL-R (i.e.,

more SNS activation; $\Delta SCL > 6.53$; 3.2% of participants), the association between family stress and IL-6 was positive and significant. For youths with low SCL-R (i.e., less SNS activation; $\Delta SCL \leq 6.53$; 96.8% of participants), this association was not significant. This result suggested that high SNS activation indicated by SCL-R exacerbated low-grade inflammation among youths who experienced higher levels of harsh parenting.

The right columns of Table 2 and Panel (C) of Figure 2 present the moderating effect of PEPr-R on the effect of family stress on inflammatory indices. Results indicated that the latent interaction factor of harsh parenting and $\Delta PEPr$ was significantly associated with higher levels of IL-6 ($\beta = -.40$, 95% *CI* $[-.45, -.003]$, $p = .018$) and CRP ($\beta = -.35$, 95% *CI* $[-.16, -.02]$, $p = .009$). Figure 5 presents the interpretation of the moderating effect of $\Delta PEPr$ on the associations between family stress and IL-6 levels. Specifically, for youths with high PEPr-R (i.e. more SNS activation; $\Delta PEPr \leq -1.50$; 5.4% of participants), the association between family stress and IL-6 was positive and significant. For youths with low PEPr-R (i.e. less SNS activation; $\Delta PEPr > -1.50$; 94.6% of participants), the association between harsh parenting and IL-6 levels was non-significant. Figure 6 presents the interpretation of the moderating effect of $\Delta PEPr$ on the associations between family stress and CRP levels. For youths with high PEPr-R (i.e. more SNS activation; $\Delta PEPr \leq -5.10$; 1.1% of participants), the association between family stress and CRP levels was positive and significant. For youths with low PEPr-r (i.e. less SNS activation; $\Delta PEPr > 0.00$; 54.8% of participants), harsh parenting and CRP levels were negative and significant. Overall, the results found high SNS activation indicated by PEPr-R as a risk factor for systemic inflammation among youth who reported harsh parenting.

Discussion

Youths who grow up in harsh rearing environments experience chronic stress that, in turn, is associated with health risks across the lifespan (Miller & Chen, 2010). The findings from the present study corroborate and advance knowledge on the effects of family stress on a youth's health risk. First, this study provides support for biological sensitivity to context theoretical models (Boyce & Ellis, 2005; Ellis & Boyce, 2008; Obradović et al., 2010) among an ethnically diverse and impoverished sample of youth. In particular, the risk incurred by family stress on the immune system in childhood (McEwen & Stellar, 1993; Nusslock & Miller, 2016) varied by level of ANS functioning. We found that the link between family stress and heightened inflammation was intensified by the sympathetic (SCL-R and PEPr-R) and buffered by the parasympathetic (HRV-R) nervous systems. Because the ANS is amenable for change via behavioral intervention (e.g., mindful meditation Tang et al., 2009), there are important prevention implications for unpacking the moderating role of the ANS as a biologically embedded context in the association between family stress and inflammatory response (Chiang, Taylor, & Bower, 2015).

Extant research shows that youths who were reared in a harsh family environment experience significant psychological and physiological stress (El-Sheikh & Erath, 2011; Repetti, Robles, Reynolds, & Sears, 2012). Through repetitive harsh interactions between the child and the parent, the child continuously endures stress associated with the chronic presence of a persistent threat. Recent advances in developmental psychobiology and evolutionary developmental perspectives suggest that prolonged exposure to stressors may culminate in neurobiological adaptations to one's context (i.e., biological sensitivity to context; Boyce & Ellis, 2005; Del Giudice, Ellis, & Shirtcliff, 2011; Shonkoff, Boyce, & McEwen, 2009). Research suggests that youths' ANS responses are dynamically shaped by the interaction between

experiences, such as parenting, and the biological stress response system, which is consolidated in adolescence. Thus, the stress response system may act as a biological moderator that influences the effect of parenting stress on child health.

Testing the biological sensitivity theories in relation to parenting and health risk using psychophysiological data is particularly lacking among minority youth (Gatzke-Kopp, 2016). Past research suggests a differential effect of firm and authoritative parenting on youth adjustment across cultures. For example, in risky contexts, among low-SES African American families, firm and authoritative parenting is more effective in reducing problem behaviors than in safer environments (Brody, Dorsey, Forehand, & Armistead, 2002; Pettit, Bates, Dodge, & Meece, 1999; Shumow, Vandell, & Posner, 1998). It is possible that differential ANS sensitivity to parenting context may explain why, for some youth, more authoritative and firm parenting can still be linked to less harmful outcomes. However, in the present study harsh parenting and not firm was examined. Thus, our study suggests that harsh parenting behaviors, represented by corporal punishment and psychological aggression, also bears an adverse effect on health among minority youth.

Our first hypothesis was partially supported in that the effect of harsh parenting on elevated systemic inflammation among children was evident only at specific levels of ANS functioning, and this was more prevalent for IL-6 than CRP. Using a larger sample, Slopen et al. (2013) reported significant associations between cumulative early adversity and elevation of both CRP and IL-6. However, these effects were very small in size (β s are $< .1$), possibly suggesting that the present study lacks the statistical power to consistently detect significant inflammation effects on both IL-6 and CRP. Similarly, a recent meta-analysis on the effect of early-life adversity on pro-inflammatory phenotypes in adulthood revealed differential associations

between childhood stress and adulthood elevations in CRP and IL-6, depending on the type of reported childhood stressors (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016). In the present study, types of family stress that the child experienced were not assessed, precluding the ability to examine these expected differences between early adversity and inflammation.

Our second hypothesis was also supported in that the ANS system modulated the impact of family stress on youth inflammation. The findings on the moderating role of the ANS in the link between harsh parenting and increased inflammation corroborates research and theory on the interaction between the peripheral nervous system and the immune system (Nelson et al., 2017). Although the connection between vagal nerve activity and the inflammatory response has been mostly shown in animal research (Kemp & Quintana, 2013), growing research has shown this link in human populations (von Känel, Carney, Zhao, & Whooley, 2011). The ANS and the inflammatory response are intimately linked, and sympathetic and parasympathetic nervous pathways are thought to have anti-inflammatory functions (Pavlov et al., 2009; Thayer, 2009). Previous reports also show that the SNS has pro-inflammatory effects, while the PNS has anti-inflammatory effects (Fagundes & Way, 2014; Thayer & Sternberg, 2006). The vagus nerve, for example, targets different organs, including the spleen, where monocytes and macrophages are located, controlling the inflammatory response (Pavlov & Tracey, 2012). This body of research supports the notion of an *inflammatory reflex* mechanism in which the ANS modulates the inflammatory response on a moment-to-moment basis (Williams et al., 2019). According to this line of research, the vagus nerve bi-directionally connects the brain and immune system to attenuate excessive inflammation processes exterior to the CNS. Thus, through its activation of the efferent arm, the vagus nerve has an immunomodulatory function for regulating cytokine production (Johnston & Webster, 2009). Increased understanding of the risky or protective role

of the ANS in the association between family stress and low-grade inflammation can help preventive interventions that target the ANS. Increasing HRV through psychosocial intervention may help mitigate health risks incurred by family stress (Streeter, Gerbarg, Saper, Ciraulo, & Brown, 2012).

Limitations

The present study has some limitations. First, this is a cross-sectional pilot study, and the absence of longitudinal data prevents us from drawing a conclusion about the long-term link between family stress and low-grade inflammation in youth. Because we recruited low-income families and sampled a high rate of minorities, we are uncertain whether the findings in the present study would generalize to children from other racial/ethnic backgrounds. However, the findings provide further validation to differential biological sensitivity to parenting and attendant inflammation risk among minority and impoverished youth. Further, the modest sample size ($N = 101$) limited our statistical power to test study hypotheses. This may explain the lack of significant direct effects from parenting to inflammation risk, and the tenuous interaction revealed with PEPr in predicting elevations in CRP. Yet, power analyses revealed excellent power of the moderating roles of HRV and PEPr but showed moderate power of the moderating effect of SCL on the associations between harsh parenting and inflammation. Lastly, we did not obtain data about youths' medication use, so we are unable to rule out the possibility of the influence of stimulant medication on ANS functioning. Despite these limitations, this study includes significant methodological strengths, including the use of serum to obtain measures of inflammation from children, a behavioral task to elicit acute family stress to measure ANS activity, and the sampling of understudied populations.

Conclusions

A large body of research shows that family stress, such as the stress induced by harsh parenting, may give rise to health problems in youth. The present study sought to show that this association varies by youths' biological stress response. Accordingly, the link between harsh parenting and inflammation risk may be modified per youth biological response to stress reactivity as indicated by the ANS. Indeed, markers of the PNS (HRV-R) and SNS (SCL-R & PEPr-R) were tested as moderators and found to significantly attenuate and exacerbate, respectively, the link between exposure to harsh parenting and low-grade inflammation among a sample of youths. These findings provide support for the biological sensitivity to context theory, generating evidence that the stress response system can significantly modify the risk that adverse environments have on health. Moreover, these results provide further support for prevention and intervention efforts. Specifically, prevention and intervention programs targeting the ANS may attenuate the health risk incurred to youth through exposure to harsh family environments.

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Table 1. *Descriptive Statistics and Correlations of Study Variables (N = 101)*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. HP-Corporal punishment	--													
2. HP -Psychological Aggression	.43**	--												
3. HP -Weekly Discipline	.47**	.44**	--											
4. HP -Neglect	.45**	.23*	.38**	--										
5. CRP	-.04	-.06	-.16	.01	--									
6. IL-6	.18	.10	.20	-.12	.13	--								
7. ΔHRV	.04	.14	-.01	-.07	.07	.18	--							
8. ΔSCL	-.06	-.11	-.01	.11	-.07	-.08	-.20	--						
9. ΔPEPr	-.08	-.13	.02	.00	.02	-.05	.06	-.04	--					
10. Waist circumferences	.04	.19	.27**	.03	.59**	.15	.07	-.08	-.01	--				
11. Youth age	.06	.24*	.17	.03	-.02	.06	.24*	-.07	.08	.44**	--			
12. Systolic blood pressure	.02	-.07	.02	-.04	.22	.03	.15	-.01	-.02	.39**	.32**	--		
13. Diastolic blood pressure	-.02	-.03	-.05	-.06	.28*	-.01	.04	-.03	.02	.18	.19	.68**	--	
14. Resting heart rate	.04	-.03	-.07	-.03	.06	.03	.21*	-.02	-.03	-.02	-.17	.22*	.22*	--
Mean	8.16	21.74	5.05	3.66	1.28	5.26	-.30	3.09	0.08	71.08	10.28	108.12	64.90	84.24
SD	14.79	22.39	7.85	10.43	1.89	3.98	1.36	1.75	1.33	13.17	1.19	10.56	7.32	11.94

Note. HP = Harsh Parenting; ΔHRV = Heart rate variability change score; ΔSCL = Skin conductance level change score; ΔPEPr = Pre-ejection period change score. For CRP and IL-6 levels, the mean and *SD* of transformed values are presented in mg/L. * $p < .05$; ** $p < .01$

Table 2.

Models of Moderating Roles of HRV, Skin Conductance, and Impedance Reactivity on the Associations Between Conflict Tactics Scale and Inflammation.

Paths	Heart Rate Variability Model			Skin Conductance Model			Impedance Model		
	<i>B (SE)</i>	β	95%CI of <i>B</i>	<i>B (SE)</i>	β	95%CI of <i>B</i>	<i>B (SE)</i>	β	95%CI of <i>B</i>
Direct Effects									
HP → IL-6	.220 (.143)	.592	[-.061, .455]	.130 (.201)	.199	[-.264, .461]	.032 (.092)	.097	[-.148, .213]
ΔHRV → IL-6	.042 (.030)	.137	[-.017, .100]	--	--	--	--	--	--
ΔSCL → IL-6	--	--	--	-.115 (.174)	-.092	[-.455, .226]	--	--	--
ΔPEPr → IL-6	--	--	--	--	--	--	.022 (.036)	.075	[-.048, .092]
HP → CRP	-.121 (.113)	-.208	[-.343, .066]	-.045 (.143)	-.054	[-.325, .191]	-.228 (.115)	-.395	[-.454, -.003]*
ΔHRV → CRP	.016 (.036)	.033	[-.056, .076]	--	--	--	--	--	--
ΔSCL → CRP	--	--	--	-.035 (.109)	-.022	[-.250, .179]	--	--	--
ΔPEPr → CRP	--	--	--	--	--	--	.075 (.055)	.148	[-.033, .183]
Interaction Effect									
ΔHRV X HP → IL-6	.101 (.037)	.366	[.028, .161]**	--	--	--	--	--	--
ΔSCL X HP → IL-6	--	--	--	.347 (.155)	.261	[.043, .651]*	--	--	--
ΔPEPr X HP → IL-6	--	--	--	--	--	--	-.088 (.037)	-.349	[-.161, -.015]*
ΔHRV X HP → CRP	.032 (.038)	.075	[-.043, .107]	--	--	--	--	--	--
ΔSCL X HP → CRP	--	--	--	-.186 (.142)	-.110	[-.463, .092]	--	--	--
ΔPEPr X HP → CRP	--	--	--	--	--	--	-.107 (.041)	-.246	[-.187, -.027]**
Control									
WC → IL-6	.004 (.004)	.130	[-.004, .012]	.005 (.006)	.118	[-.007, .018]	.002 (.004)	.075	[-.006, .010]
Youth age → IL-6	.012 (.042)	.035	[-.071, .095]	.034 (.064)	.067	[-.091, .159]	.044 (.044)	.135	[-.043, .130]
Systolic BP → IL-6	-.013 (.007)	-.639	[-.027, .001]	-.017 (.066)	-.061	[-.146, .113]	-.002 (.004)	-.115	[-.010, .005]
Diastolic BP → IL-6	.014 (.034)	.065	[-.053, .081]	-.048 (.259)	-.035	[-.556, .460]	.003 (.042)	.015	[-.079, .085]
Resting HR → IL-6	.050 (.036)	.231	[-.020, .121]	.204 (.199)	.177	[-.187, .595]	.100 (.170)	.123	[-.233, .433]
WC → CRP	.040 (.006)	.828	[.028, .052]***	.043 (.007)	.748	[.029, .058]***	.040 (.006)	.794	[.028, .051]***
Youth age → CRP	-.131 (.044)	-.243	[-.218, -.045]**	-.135 (.051)	-.209	[-.235, -.035]**	-.124 (.046)	-.220	[-.213, -.034]**
Systolic BP → CRP	-.001 (.005)	-.016	[-.011, .010]	-.056 (.041)	-.163	[-.136, .023]	.005 (.005)	.147	[-.004, .014]
Diastolic BP → CRP	-.086 (.040)	-.256	[-.165, -.008]*	-.384 (.200)	-.224	[-.775, .007]	-.074 (.045)	-.211	[-.162, .014]
Resting HR → CRP	.041 (.040)	.121	[-.037, .119]	.155 (.173)	.106	[-.0183, .493]	-.008 (.176)	-.006	[-.352, .336]
Model fit indices									
$\chi^2(35) = 46.714$ ($p = .089$), CFI = .940, RMSEA = .058				$\chi^2(37) = 45.044$ ($p = .171$), CFI = .958, RMSEA = .047			$\chi^2(34) = 34.634$ ($p = .438$), CFI = .997, RMSEA = .014		

Note. SE = Standard error; CI = Confidence interval; HP = Harsh Parenting; ΔHRV = Heart rate variability change score; ΔSCL = Skin conductance level change score; ΔPEPr = Pre-ejection period change score; WC = Waist circumferences; BP = Blood pressure; HR = Heart rate. * $p < .05$; ** $p < .01$; *** $p < .001$.

Figure 1. Conceptual Model.

Figure 2. Moderating Roles of ANS on Youth Systemic Inflammation.

Note. Panel (A) shows the moderating role of HRV on inflammation. Panel (B) shows the moderating role of SCL on inflammation; Panel (C) shows the moderating role of PEP on inflammation. In all three models, children's age, waist circumference, systolic and diastolic blood pressure, and resting heart rate were controlled. Standardized coefficients are presented in the figure. Δ HRV = Heart rate variability change score; Δ SCL = Skin conductance level change score; Δ PEPr = Pre-ejection period change score.

Figure 3. Interpretation of the Moderating Role of the HRV Reactivity on the Effect of Family Stress on Youth IL-6.

Note. The upper panel presents an adapted simple slope interpretation, and the lower panel presents the Johnson-Neyman plot. In both figures, shadowed area indicates region of significance. The solid line represents a moderate HRV reactivity level that is one boundary of significant region ($\Delta\text{HRV} = 1.15$, Slope $b = .35$, $p = .05$). The dotted line represents the low extreme of HRV reactivity level that is one boundary of the significant region ($\Delta\text{HRV} = 4.54$, Slope $b = .70$, $p < .001$). The long dash dot line represents the high HRV reactivity level (one SD from the mean) where the effect is not significant ($\Delta\text{HRV} = -1.66$, Slope $b = .08$, $n.s.$).

Figure 4. Interpretation of the Moderating Role of the SCL Reactivity on the Effect of Family Stress on Youth IL-6.

Note. The upper panel presents an adapted simple slope interpretation, and the lower panel presents the Johnson-Neyman plot. In both figures, shadowed area indicates region of significance. The solid line represents a moderate SCL reactivity level that is one boundary of significant region ($\Delta SCL = 6.53$, Slope $b = .32$, $p = .05$). The dotted line represents the high extreme of SCL reactivity level that is one boundary of the significant region ($\Delta SCL = 9.18$, Slope $b = .40$, $p < .01$). The long dash dot line represents the low SCL reactivity level that (one SD from the mean) where the effect is not significant ($\Delta SCL = 1.25$, Slope $b = -.03$, $n.s.$).

Figure 5. Interpretation of the Moderating Role of the PEPPr Reactivity on the Effect of Family Stress on Youth IL-6.

Note. The upper panel presents an adapted simple slope interpretation, and the lower panel presents the Johnson-Neyman plot. In both figures, shadowed area indicates region of significance. The dotted line represents a moderate PEPPr reactivity level that is one boundary of significant region ($\Delta\text{PEPr} = -1.50$, Slope $b = .17$, $p = .05$). The dash line represents the high extreme of PEPPr reactivity level that is one boundary of the significant region ($\Delta\text{PEPr} = -5.48$, Slope $b = .55$, $p < .001$). The long dash dot line represents the low PEPPr reactivity level that (one SD from the mean) where the effect is not significant ($\Delta\text{PEPr} = 1.41$, Slope $b = -.10$, n.s.).

Figure 6. Interpretation of the Moderating Role of the PEPr Reactivity on the Effect of Family Stress on Youth CRP.

Note. The upper panel presents an adapted simple slope interpretation, and the lower panel presents the Johnson-Neyman plot. In both figures, shadowed area indicates region of significance. The dotted line represents a moderate high PEPr reactivity level that is one boundary of the positive significant region ($\Delta\text{PEPr} = -5.10$, Slope $b = .33$, $p = .05$). The dash line represents the high extreme of PEPr reactivity level that is one boundary of the positive significant region ($\Delta\text{PEPr} = -5.48$, Slope $b = .40$, $p < .05$). The long dash dot line represents the moderate low PEPr reactivity level that is one boundary of the negative significant region ($\Delta\text{PEPr} = .00$, Slope $b = -.24$, $p = .05$). The long dash double dot line represents the low extreme of PEPr reactivity level that is one boundary of the negative significant region ($\Delta\text{PEPr} = 5.93$, Slope $b = -.90$, $p < .001$).

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