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Early caregiving stress exposure moderates the relation between respiratory sinus arrhythmia reactivity at 1 month and biobehavioral outcomes at age 3

ELISABETH CONRADT,[a] THEODORE BEAUCHAINE,[b] BEAU ABAR,[c] LINDA LAGASSE,[d,e] SEETHA SHANKARAN,[f] HENRIETTA BADA,[g] CHARLES BAUER,[h] TONI WHITAKER,[i] JANE HAMMOND,[j] AND BARRY LESTER[d,e]

[a]Department of Psychology, University of Utah, Salt Lake City, Utah, USA
[b]Department of Psychology, Ohio State University, Columbus, Ohio, USA
[c]Departments of Emergency Medicine, Psychiatry, and Public Health Services, University of Rochester Medical Center, Rochester, New York, USA
[d]Department of Pediatrics, Women and Infants Hospital of Rhode Island, Providence, Rhode Island, USA
[e]Departments of Psychiatry and Pediatrics, Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA
[f]Department of Pediatrics, Wayne State University School of Medicine, Detroit, Michigan, USA
[g]Department of Pediatrics, University of Kentucky College of Medicine, Lexington, Kentucky, USA
[h]Department of Pediatrics, University of Miami Miller School of Medicine, Miami, Florida, USA
[i]Department of Pediatrics, University of Tennessee Health Science Center, Memphis, Tennessee, USA
[j]RTI International, Research Triangle Park, North Carolina, USA

Abstract

There is a growing scientific interest in the psychophysiological functioning of children living in low-socioeconomic status (SES) contexts, though this research is complicated by knowledge that physiology–behavior relations often operate differently in these environments among adults. Importantly, such research is made more difficult because SES may be a proxy for a wide range of risk factors including poor caregiving and exposure to parental substance use. We used factor analysis to organize risk-exposure data collected from 827 children—many of whom were raised in low-SES contexts and exposed to substances prenatally—into dissociable components including economic stress, caregiving stress (e.g., stress the caregiver may experience, including parental psychopathology), and postnatal substance exposure. These factors, along with respiratory sinus arrhythmia (RSA) reactivity at age 1 month, were used to predict behavior dysregulation and resting RSA at age 3 years. A significant RSA Reactivity × Caregiving Stress interaction indicated that infants who exhibited high RSA reactivity at 1 month experienced the greatest behavior dysregulation at 3 years, but only when they were exposed to high levels of caregiving stress. Among African Americans, the highest resting RSA at 3 years was found in infants with less RSA reactivity, but only if they also experienced less caregiving stress. Our work is consistent with biological sensitivity to context, adaptive calibration, and allostatic load models, and highlights the importance of studying Physiology × Environment interactions in low-SES contexts for predicting behavior and resting RSA.

Descriptors: Individual differences, Infants/children, Heart rate

Socioeconomic status (SES) is a potent indicator of human health, with effects on both physiological and behavior development (Boyce, Sokolowski, & Robinson, 2012; Kishiyama, Boyce, Jimenez, Perry, & Knight, 2008). However, very little is known about psychophysiological functioning among children who live in low-SES contexts, although it is recognized that physiological biomarkers may aid in the identification of who is most sensitive to such environments (Boyce & Ellis, 2005). Most researchers operationalize SES as a composite of income, education, and occupation (Adler et al., 1994; Bradley & Corwyn, 2002). Oftentimes, SES is treated as a "nuisance" variable in psychophysiological research. In fact, researchers often use it as a statistical control variable when they examine physiology–behavioral relations. One reason that SES is rarely used as a predictor of physiological processes is because it is not directly causal. Rather, it is a proxy for

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Address correspondence to: Elisabeth Conradt, University of Utah, 380 S. 1530 E. BEHS 602, Salt Lake City, UT 84112. E-mail: elisabeth.conradt@psych.utah.edu

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unmeasured variables that exert direct effects on physiological and behavioral functioning. Low SES is associated with risk factors such as parental mental and physical health, exposure to parenting stress, prenatal and postnatal drug exposure, and neighborhood violence and criminality (Brooks-Gunn & Duncan, 1997). Models that include these variables are needed to identify processes through which some children who are reared in low-SES contexts develop poor behavioral and physiological outcomes.

To date, most researchers, including our own group, have examined how early-life stress affects brain and behavior development using a cumulative-risk approach (Conradt et al., 2014). This strategy derives in part from the observation that although overlapping, risk factors are not entirely redundant (e.g., Conradt, Measelle, & Ablow, 2013; Evans & Kim, 2012). Cumulative-risk models are therefore more powerful than single-risk models in predicting problem behavior, particularly among children with prenatal substance exposure (Yumoto, Jacobson, & Jacobson, 2008). Importantly, however, the type of early-life stress experienced may exert unique effects on central nervous system (CNS) and parasympathetic nervous system (PNS) development, even when controlling for associated risk factors. PNS function is indexed by respiratory sinus arrhythmia (RSA). RSA consists of oscillatory increases and decreases of heart rate across the respiratory cycle (see Beauchaine, 2001, 2015). This heart rate variability is controlled by a cardiorespiratory source generator that projects from the CNS to the heart through the 10th cranial (vagus) nerve (Berntson et al., 1997; Grossman, 1983; Porges, 2007). In their review of the literature on proximal risk factors and ANS development, Propper and Holochwost (2013) concluded that environmental risk factors, such as low SES, may exert negative effects on brain and behavior through more proximal risk factors, such as parenting. Among children with prenatal substance exposure, postnatal caregiver substance use may be one such parenting behavior that is associated with poor child behavioral outcomes (Mayet et al., 2008). For instance, Hickey, Suess, Newlin, and Spurgeon (1995) found that performance on an attention task was lowest among boys with prenatal opiate exposure and boys with no prenatal drug exposure but whose parents used opiates postnatally, compared to boys with no prenatal or postnatal exposure. Prenatal parental substance use is also predictive of postnatal use, which in turn is associated with child foster care placement (Smith, Johnson, Pears, Fisher, & DeGarmo, 2007). In turn, child maltreatment is a risk factor for impaired CNS and ANS functioning (see, e.g., Beauchaine & McNulty, 2013). For instance, Skowron, Cipriano-Essel, Gatzke-Kopp, Teti, and Ammerman (2014) found that better inhibitory control was predicted by RSA withdrawal, but only for nonmaltreated children. High inhibitory control among children who were maltreated was instead predicted by increased RSA from baseline to task (Skowron et al., 2014).

Another risk factor common to children with prenatal substance exposure is maternal depression (Mayet et al., 2008). Depressed mothers tend to interact insensitively with their children, who in turn do not exhibit age-expected increases in resting RSA during early childhood (Field et al., 2004). In a sample of depressed mothers who are exposed to contextual risk factors such as family stress and low social support, those with chronic depression when their children were ages 14 months to 6.5 years had children with greater RSA reactivity at age 6.5 (Ashman, Dawson, & Panagiotides, 2008). Such patterns of RSA reactivity are frequently associated with internalizing and externalizing psychopathology (see Beauchaine, 2001, 2015; Beauchaine & Thayer, 2015). Exposure to a caregiver who may be stressed is therefore of great concern given its associations with impaired parasympathetic functioning and psychopathology.

Poverty is also of concern. The more time children spend living in poverty, the more blunted their blood pressure responses are to stress at age 13, over and above effects of current poverty (Evans & Kim, 2007). Furthermore, greater household density is related to greater blood pressure and heart rate reactivity among fifth and sixth graders (Johnston-Brooks et al., 1998). Although researchers have investigated effects of parenting on PNS function among mothers who live in poverty (e.g., Conradt & Ablow, 2010; Propper et al., 2008), we know of no studies that have compared proximal (e.g., stress that may affect the caregiving environment; Propper & Holochwost, 2013), and distal (e.g., economic stress) risk factors on autonomic and behavioral outcomes. Such study comparisons are critical if we wish to (i) understand how discrete risk factors affect physiological and behavioral outcomes, and (ii) formulate more effective prevention and intervention programs (see Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008).

In addition to identifying types of risk factors that affect physiology and behavior, we also seek to determine which stressors may be more detrimental than others at certain developmental periods (Miller, Chen, & Zhou, 2007). In other words, the timing of exposure to low-SES conditions may be important in predicting brain–behavior outcomes. For example, poverty experienced in early childhood is particularly detrimental to emotional and behavioral health compared to poverty experienced in middle childhood or adolescence (Brooks-Gunn & Duncan, 1997). Mechanisms (e.g., malnutrition or poor parental care) responsible for such effects are less clear. According to Hertzman (1999), stressful early-life experiences may become "biologically embedded" to affect stress response system functioning and in turn behavioral responses to stress. Two partially overlapping theoretical perspectives suggest how such biological embedding may occur: the allostatic load and adaptive calibration models. The purpose of this brief review is to provide a framework from which to understand how physiology–physiology and physiology–behavior associations may be affected by SES. An excellent review comparing, contrasting, and providing detailed descriptions of these theories can be found in Hostinar and Gunnar (2013).

According to these perspectives, physiological responses to stress are usually adaptive in the short term (Boyce & Ellis, 2005; Bush & Boyce, 2014; Del Giudice, Ellis, & Shirtcliff, 2011; McEwen & Gianaros, 2010; McEwen & Stellar, 1993), and may result from adaptations to the environment in which a child is reared (Boyce & Ellis, 2005; Bush & Boyce, 2014). Allostatic load suggests that when faced with recurrent threats and stress, which may occur in low-SES contexts, repeated activation of stress response systems alters the functional operating ranges of neural systems implicated in behavioral impulsivity, mood regulation, and social affiliation (Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, 2011). These processes induce wear and tear on stress and immune system functioning, resulting in greater risk for poor psychological and physical health outcomes (McEwen & Gianaros, 2010). Functional operating ranges of certain neural systems may be inferred from baseline physiological functioning (e.g., Beauchaine et al., 2011; El-Sheikh & Hinnant, 2011). In other words, histories of repeated adversity and stress exposure alter physiological functioning at rest (McEwen & Stellar, 1993). Over time, recurrent threatening experiences, associated vigilance, and feelings of helplessness contribute to an individual's perception of new situations as stressful, which in turn initiates a dynamic cascade of

behavioral and physiological stress responses that are no longer adaptive when they result in protracted or even permanent alterations in physiological functions (El-Sheikh & Hinnant, 2011; McEwen & Stellar, 1993). The adaptive calibration model (Del Giudice et al., 2011) is an extension of biological sensitivity to context theory (Boyce & Ellis, 2005). It suggests that individual differences in stress responding result from adaptations to particular environments in which an individual is reared. Over time, and if environmental conditions change, the stress response system adapts and feeds back to recalibrate its functional operating range, if necessary. Importantly, high physiological reactivity may be adaptive according to this framework, if children with high reactivity are raised in supportive environments. The reverse is true, however, if high-reactive children are reared in negative, threatening, and impoverished contexts (Boyce & Ellis, 2005).

Such effects may be direct or mediated through relationships with primary caregivers. As noted above, children reared in low-SES environments are often exposed to maternal depression, which renders mothers less responsive to bids for comfort and reassurance (Bradley & Corwyn, 2002; Harnish, Dodget, & Valente, 1995). These experiences may in turn result in increased autonomic activity/reactivity among affected children (Conradt & Ablow, 2010). According to the allostatic load perspective, if such experiences recur often enough throughout development, multiple "hits" to the ANS may lead to a downregulated stress response (see Beauchaine et al., 2011; El-Sheikh & Hinnant, 2011; McEwen & Stellar, 1993).

Such models provide a framework through which to understand some important discrepancies in the psychophysiological literature. For example, although it is generally assumed that higher resting levels of RSA are adaptive throughout development (see Beauchaine, 2001, 2015; Beauchaine, Gatzke-Kopp, & Mead, 2007), higher resting RSA may not predict positive outcomes in low-SES samples or in very young children (Conradt et al., 2013; Holochwost, Gariepy, Propper, Mills-Koonce, & Moore, 2014). Such findings may support the biological sensitivity to context model. For instance, toddlers who are raised in low-SES environments who receive insensitive caregiving have the highest levels of problem behavior, but only if they also exhibit high resting RSA (Conradt et al., 2013). Inattention to demographic factors may therefore obscure physiology–physiology and physiology–behavior outcomes (see Gatzke-Kopp, 2016).

Accordingly, a more complete understanding of stress responding in low-SES environments may be needed to identify responses that are problematic. Using the aforementioned example, in ordinary environments, high resting RSA is associated with better self-regulation, social competence, and empathy (Beauchaine, 2001, 2015). In contrast, in low-SES contexts it may only predict adaptive outcomes among infants and children who are raised by supportive caregivers (Conradt et al., 2013). Specific measures of the type of environment in which children are raised are needed to test processes through which environments interact with physiological functioning in children, which in turn may affect relevant brain/behavior relations. Such information in turn may allow us to use physiological markers to identify children who are vulnerable to later problem behavior, particularly in low-SES contexts (Beauchaine et al., 2008).

We collected measures of children's RSA in predominantly low-SES environments. Seventy-nine percent of these children were drug exposed prenatally. RSA was chosen because far less is known about how RSA functions in low-SES environments in childhood compared to the sympathetic or neuroendocrine systems, and past research indicates it is sensitive to stressful experiences (El-Sheikh & Hinnant, 2011; Propper, 2013). High resting RSA is thought to reflect neural integrity and readiness to respond to environmental stressors (Beauchaine, 2001, 2015; Porges, 1995). Change in RSA in response to environmental stimulation and challenge is termed RSA reactivity. We studied effects of RSA reactivity at age 1 month because both allostatic load and adaptive calibration models indicate that the way in which an organism responds to stress may be a stronger predictor of later behavioral and physiological outcomes than basal or resting physiological measures. Our outcomes included behavior dysregulation and resting levels of RSA at age 3 years. We calculated a behavior dysregulation composite, rather than examine internalizing and externalizing behavior separately, because (i) at age 3, differences in internalizing and externalizing behavior may not be as pronounced in later childhood (Essex, Klein, Cho, & Kalin, 2002; Rose, Rose, & Feldman, 1989); and (ii) the correlation between internalizing and externalizing behavior was strong and positive.

Present Study

Before embarking on our main study aims, we conducted exploratory and confirmatory factor analyses of variables thought to index SES, and variables known to covary with SES, to determine whether type of stress exposure was related to behavioral and physiological outcomes. Although SES itself does not cause adversity (see above), we included variables traditionally thought to index SES in order to examine effects of our stressors above and beyond SES, and because SES may reflect variables that were not measured in this study (such as family discord). We hypothesized that dissociable factors would emerge, representing the range of stressors to which children with prenatal drug exposure may experience (e.g., exposure to parental psychopathology, parental stress, lack of monetary resources, postnatal substance exposure; Dong et al., 2004). Next, we examined main effects and interactions between stress variables experienced between birth and age 1 year, and behavior dysregulation and resting RSA at age 3 years. Although no studies have examined effects of one type of stressor, over and above others, given the centrality of the caregiving environment in early childhood, and the comparatively larger body of work indicating associations between caregiving and psychophysiology in low-SES samples, we expected that caregiving insufficiency would exert a stronger influence on physiological and behavioral outcomes in early childhood than economic insufficiency or even postnatal caregiver drug use. Furthermore, based on both the allostatic load and adaptive calibration models, in addition to work implicating prior experiences of stress reactivity with later resting physiology (El-Sheikh & Hinnant, 2011), we expected that the combination of exposure to stress and physiological reactivity during the first year of life would predict greater behavior dysregulation, and lower resting RSA by age 3 years.

Method

Participants

We used data from participants in the Maternal Lifestyle Study (MLS), a multisite investigation of effects of prenatal substance exposure in a longitudinal follow-up from 1 month to 16 years. Mother–infant dyads from singleton gestations were recruited between May 1993 and May 1995. Maternal exclusion criteria included age <18 years, psychosis or history of institutionalization for intellectual disability or emotional problems, and language

barriers that prevented them from giving informed consent or understanding the study. All participants spoke English. Infant inclusion criteria included viable, singleton birth, birth weight of at least 500 g, gestational age less than 43 weeks by best obstetric estimate, and a negative screen for chromosomal abnormality or TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis).

Participants were recruited from Detroit, MI; Memphis, TN; Miami, FL; and Providence, RI. A total of 19,079 mother–infant dyads were screened for study recruitment. From these, 16,988 dyads were eligible for enrollment, and 11,811 (70%) gave consent. Of these, 1,072 infants were cocaine exposed. A list of possible comparison infants (matched on race, sex, and gestational age) was sent by the data center to each study site. Mothers were called on the list in sequence to confirm consent for the 1-month visit. When an infant in the comparison group did not attend the 1-month visit, another match was generated for each exposed infant until a comparison infant was successfully enrolled in the 1-month visit. This procedure resulted in two groups at the 1-month visit: 658 cocaine-exposed infants (61.4% retention of the cocaine-exposed group) and 730 infants without cocaine exposure ($N = 1{,}388$).

Mothers were approached in the hospital following delivery, informed consent was obtained, and mothers were interviewed for history of smoking, alcohol use, and drug use during pregnancy and in the last year. Meconium was collected from the newborn in order to conduct toxicology screens for cocaine or opiate metabolites. Families were selected for the exposed group (i.e., maternal report of cocaine or opiate use during pregnancy or gas chromatography–mass spectrometry confirmation of presumptive positive meconium screens for cocaine or opiate metabolites) or the comparison group (i.e., maternal denial of cocaine or opiate use during the pregnancy and a negative enzyme multiplied immunoassay meconium screen for cocaine and opiate metabolites). If a woman denied use of cocaine during pregnancy but mass spectrometry results were positive for cocaine exposure then the child was considered cocaine exposed. Exposed and comparison youth were group matched on race, sex, and gestational age within each study site. Background substances associated with cocaine use (alcohol, tobacco, and marijuana) were present in both groups; thus, most participants were polysubstance exposed. However, a subset of infants (21.3%) was not exposed to any substances in utero. Although the original intent of the study was to examine effects of cocaine exposure on psychosocial outcomes, the purpose of this study was to examine effects of early-life stress in a low-SES context and psychophysiology on behavioral and physiological outcomes. We therefore included cocaine exposure and postnatal caregiver cocaine use as covariates in all analyses but did not explore main effects of cocaine exposure. The study was approved by the institutional review board at each study site, and written informed consent (from caregivers) was obtained for all participants. Each site had a certificate of confidentiality from the National Institute on Drug Abuse.

The MLS sample includes children in the following racial categories: African American (77%), Caucasian (16%), Hispanic (6%), and children whose parents identified other racial backgrounds (1%). There were significantly more African American and Hispanic participants in Detroit, and more Caucasians in Providence compared to the other sites, $\chi^2\,(9) = 299.42$, $p < .001$.

Measures

Respiratory sinus arrhythmia (RSA). At 1 month, RSA was assessed prior to and during the Neonatal Intensive Care Unit (NICU) Neonatal Network Neurobehavioral Scale (NNNS). The NNNS was administered between 42–44 weeks post menstrual age and is a standardized comprehensive evaluation of the neurobehavioral performance of high-risk term and preterm infants that includes neurological and behavioral measures and signs of stress (Lester & Tronick, 2004). Psychometric properties of the exam have been established (Lester & Tronick, 2004). The NNNS was administered by certified psychometrists blinded to exposure status. For the resting period, RSA was measured while the infant was in a quiet awake state (state 4 on the NNNS) for at least 2 min ($M = 2.23$ minutes). Measurement of RSA occurred during the NNNS visual attention procedure. This challenge task lasted, on average, 6.8 minutes ($\pm$ 2.43 min) and includes infant visual tracking to animate and inanimate stimuli. We found no significant association between the length of the challenge task and either resting RSA ($r = -.002$, $p = .95$), or RSA during the task ($r = .044$, $p = .15$). Length of assessments was not associated with any of the stress factors (all rs $\geq -.06$ and $\leq .02$, all ps $> .06$) or prenatal drug exposure ($r = .05$, $p = .11$). Estimates of RSA were averaged across the attention episode. Differences in RSA measured at rest and during the visual attention "challenge" procedure were used to calculate reactivity scores. RSA reactivity was measured as $RSA_{visual\ attention} - RSA_{rest}$. Therefore, positive scores reflect increases in RSA, whereas negative scores reflect decreases (i.e., withdrawal) in RSA.

Resting RSA was measured at age 3, while children were waiting for a mastery motivation procedure to begin. Because RSA is reduced by psychomotor activity (Porges, 2007), like others (Obradović, Bush, Stamperdahl, Adler, & Boyce, 2010), we assessed resting RSA during a nonchallenge "control" task that paralleled the motor demands of our challenge task. Use of this type of task to assess resting physiology among very young children is described by Bush, Alkon, Obradović, Stamperdahl, and Boyce (2011). Resting RSA was measured while children played with a toy alone or with an experimenter for an average of 164.8 s (range = 135.6–199.3 s). The correlation between length of the task and resting RSA was not significant, $r = -.05$, $p = .22$. Although this resting period required some attention, which may evoke moderate vagal withdrawal (see Suess, Porges, & Plude, 1994), the toy with which the child played was simple and no task demands were placed on the child. The type of activity depended on site; therefore, we control for site in our analyses. Estimates of resting RSA are similar (within 1 *SD*) to other studies of infants and young children of similar ages (Alkon et al., 2003; Calkins, Graziano, & Keane, 2007; Calkins & Keane, 2004; Doussard-Roosevelt, Montgomery, & Porges, 2003), who have also calculated RSA using the same technique.

At both time points, RSA was derived from the R-R time-series (or time between adjacent R-waves) collected from digitized electrocardiogram (ECG) recordings using Porges's MXEdit software (Delta-Biometrics Inc, 1988–1993). ECGs were recorded using three electrodes placed on the child's chest and abdomen. The ECG signal was sampled at 1 kHz and stored on a computer for later scoring. Interbeat intervals were defined by detection of R-waves to the nearest ms.

Post-processing of data took place offline by using a series of automated algorithms. These algorithms were written to identify R-R intervals outside of expected values. Missed or spurious R-waves were flagged and corrected via linear interpolation. A 21-point moving polynomial was then applied to remove low-frequency trends in the HR signal. Next, a bandpass filter extracted the variance in heart period within the frequency band of

spontaneous respiration in young children (0.24–1.04 Hz; see Zisner & Beauchaine, 2015). This process removes periodicities in the ECG signal that are outside the frequency range of the respiratory cycle. The resulting measure of RSA is in the frequency range of respiration. RSA was computed as the natural logarithm of heart period variance and reported in units of ms squared, $\ln(ms)^2$. This method was described initially by Porges (1985) and is one of several acceptable approaches for calculating RSA (Berntson et al., 1997). Spectral densities were calculated in 30 s overlapping windows and then averaged within each episode (resting period and attention task). The RSA data for an individual was used as long as there was a 30-s segment with less than 20% of segments identified with, which is the shortest duration recommended when calculating RSA (Berntson et al., 1997; Jennings et al., 1981). Specifically, if 6 s or less of RSA data were artifact, then those seconds were deleted and the rest of the RSA data from the 30-s epoch were averaged. In other words, each s was flagged and removed if 20% of the beats in that 30-s window were marked as artifact, leaving the remaining seconds to be averaged. Thirty-s epochs are frequently sampled in studies of infants and young children (Buss, Goldsmith, & Davidson, 2005; Moore & Calkins, 2004). In addition, small amounts of artifact can be expected to have a minimal effect on measures of heart rate variability, including RSA (Berntson et al., 1997).

Early-life stress indicators. Twelve variables were chosen to index early-life stress based on prior research indicating that infants with prenatal drug exposure are more likely to experience these stressors, and based on research with this population indicating that these stressors are associated with prenatal drug exposure and psychophysiological functioning (Conradt et al., 2013). These variables included the following:

Index of social position (ISP; Hollingshead, 1975). The ISP was calculated based on the formula provided by Hollingshead (1975): Parental occupation and education were coded using a 7-point scale. For parental occupation, the scale ranges from 1 (e.g., higher executives) to 7 (unskilled employees). For education, the scale ranges from 1 (e.g., professional degree) to 7 (less than 7 years of school). If there was another contributing adult in the family, then ISP was calculated by summing the average of the primary caregiver and the contributing adult's weighted education and occupation. The ISP was calculated based on the formula: (Occupation x 7) + (education x 4; Hollingshead, 1975). The ISP was reverse-scored so that higher values reflected lower ISP.

Education. A dichotomous score (1 = no, 0 = yes) was created when the infant was 1 month old based on whether or not the primary caregiver had at least a high school education.

Poverty status. Poverty status was calculated when the infant was 1 month old using the number of persons living in the household and using the Health and Human Service Poverty guidelines for the year the assessment was conducted. A dichotomous score (0 = no, 1 = yes) was created to indicate whether household income was less than $2,000/month per household member at the date of the assessment.

Caregiver symptoms of depression were assessed using the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996) at age 4 months ($\alpha = .88$). The ranges for the BDI scores were 0–56 and the score was used continuously.

Caregiver psychological distress was measured using the mean of total psychological symptoms from the Brief Symptom Inventory (BSI; Derogatis & Coons, 1993) at 4 months ($\alpha = .96$). The ranges for the BSI were 0–3.13 and continuous scores were used.

Caregiver victimization was measured using the Caretaker Inventory of Substance Use (CISU; Shankaran et al., 1996). The CISU is a caregiver-report questionnaire of current substance use and personal violence sustained by the caregiver. The caregiver indicated when the infant was 4 months and 8 months whether or not the caregiver had experienced physical or sexual abuse (0 = no, 1 = yes). The 4- and 8-month responses were averaged to reflect caregiver experience of abuse during the infant's first year of life.

Caregiver parenting stress was measured using the total score of the Parenting Stress Index (PSI; Abidin, 1990) when the infant was 4 months old. The PSI is a 36-item questionnaire, scored on a 5-point scale, administered to the caregiver. It measures parent distress, parent–child dysfunctional interaction, and the difficulty level of the child.

Caregiver postnatal tobacco use was measured using the CISU (Shankaran et al., 1996) developed by the MLS. The caregiver reported the mean number of cigarettes smoked per day. The CISU was administered at the 4-month and 8-month assessment. Scores were averaged across time points.

Caregiver postnatal alcohol use was measured by caregiver report of the mean ounces the caregiver drank per day using the CISU. Scores from the 4-month and 8-month assessment were averaged.

Caregiver postnatal marijuana use was measured by the mean number of joints the caregiver reported smoking per day using the CISU. Scores from the 4-month and 8-month assessment were averaged.

Caregiver postnatal cocaine use was measured as the number of days per week the caregiver reported using cocaine using the CISU at 4 and 8 months. Table 1 includes the percentage of caregivers who endorsed using each type of substance at least once at the 4- or 8-month assessment.

History of Child Protective Services (CPS) involvement. Caregivers were asked if there was a report to CPS made on behalf of the study child. Caregivers were interviewed by trained examiners about whether or not there had been any CPS involvement since the last visit, and if so, whether it was for sexual abuse, physical abuse, and/or neglect. If any report had been made a score of 1 was given. Scores at 1, 4, and 8 months were averaged together to create this variable.

Prenatal substance exposure. Dichotomous measures are frequently used in testing prenatal substance exposure effects (Fisher

Table 1. *Percent of caregivers engaging in postnatal substance use at 4 or 8 months*

Variable	Percent
Tobacco use	58.6
Alcohol use	61.3
Marijuana use	24.9
Cocaine use	17.2
Opiate use	0.6

Note. Tobacco use defined as percent of caregivers who smoked at least one cigarette/day when infants were 4 or 8 months old, alcohol use defined as drinking at least 1 ounce of alcohol per day at 4 or 8 months, marijuana use defined as smoking at least one joint/day when infants were 4 or 8 months old, cocaine used defined as using cocaine at least once when infants were 4 or 8 months, opiate use defined as using opiates at least once when infants were 4 or 8 months, $n = 1,259$.

Table 2. *Variable means, standard deviations, and correlations*

Variable	*M*	*SD*	n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Social position (reverse-scored)	−27.82	9.94	1364	–															
2. High school education	0.34	0.45	1363	.47***	–														
3. Poverty status	0.42	0.44	1344	.31***	.24***	–													
4. BDI	8.69	8.63	1052	.18***	.15***	.14***	–												
5. BSI	0.60	0.58	1051	.17***	.12***	.13***	.76***	–											
6. PSI	70.51	17.42	1076	.27***	.20***	.22***	.47***	.46***	–										
7. Caregiver victimization	0.08	0.22	1259	.06*	.04	.11***	.30***	.38***	.20***	–									
8. Caregiver postnatal tobacco use	6.14	8.65	1259	.17***	.12***	.04	.10**	.12***	.07*	.12***	–								
9. Caregiver postnatal alcohol use	0.22	0.62	1259	.13***	.09**	–.01	.09**	.07*	.13***	.13***	.23***	–							
10. Caregiver postnatal marijuana use	0.06	0.28	1259	.11***	.04	.04	.08**	.09**	.07*	.06*	.12***	.20***	–						
11. Caregiver postnatal cocaine use	0.03	0.17	1259	.08**	.02	.04	.09***	.10***	.07*	.11***	.14***	.18***	.09**	–					
12. Child CPS involvement	0.16	0.33	1380	–.05	.10***	–.04	–.01	.02	–.02	–.01	.01	.09***	–.06	.05	–				
13. Prenatal drug exposure	1.89	1.38	1388	.16***	.11***	.08**	.00	.06	.01	.11***	.42***	.26***	.17***	.22***	.36***	–			
14. 1 month RSA reactivity	0.12	0.71	1047	.01	.01	–.02	.02	.03	–.04	.05	.00	.04	.04	.04	–.03	.02	–		
15. Internalizing behavior (age 3)	56.12	10.61	1002	.17***	.11***	.12***	.25***	.28***	.30***	.09**	.09**	.04	.03	–.02	.06*	.06*	.03	–	
16. Externalizing behavior (age 3)	55.32	10.36	1002	.14***	.09**	.10***	.24***	.31***	.24***	.11***	.10**	.06	.04	.06	.05	.07*	.03	.77***	–
17. Resting RSA (age 3)	5.64	1.29	742	.03	.04	.04	–.13***	–.12**	.03	–.07	.03	.04	.07	.02	–.01	.08*	–.07	.04	.04

Note. BDI = Beck Depression Inventory; BSI = Brief Symptom Inventory; CPS = Child Protective Services; PSI = Parenting Stress Index; RSA = respiratory sinus arrhythmia. Socioeconomic status variables (index of social position, high school education, and income) are reverse-scored such that higher levels of these variables indicate having a lower index of social position, lower income, and are less likely to have a high school education.
*$p < .05$. **$p < .01$. ***$p < .001$.

et al., 2011). Maternal report/meconium screen of drug use (1, *yes*; 0, *no*) prenatally was computed. One point was assigned for each substance used. If a woman uses one substance while pregnant, she is more likely to use additional substances (Mayet et al., 2008). Following the work of Fisher et al. (2011) with this sample, prenatal substance exposure was measured as a summative index ranging from 0–5 for mother-reported (or gas chromatography–mass spectrometry confirmation of presumptive positive meconium screens for cocaine or opiate metabolites) use of cocaine, opiates, marijuana, alcohol, and tobacco during pregnancy.

Behavior dysregulation. The correlation between internalizing and externalizing behavior was positive and strong, $r = .77$, $p < .001$. We therefore combined internalizing and externalizing behavior to form a latent "behavior dysregulation" composite comprised of externalizing and internalizing behavior from the Child Behavior Checklist (CBCL; Achenbach, 1992), administered to caregivers when children were 3 years old. *T* scores for externalizing and internalizing behavior were used. We used *T* scores rather than raw scores because we were interested in comparing children's behavior relative to same-aged peers, normed by sex. Raw scores cannot be used to compare children's behavior against population norms of other children of the same age and sex. Caregivers rated whether each of 112 items were not true, somewhat/sometimes true, or very/often true over the past 6 months.

Missing Data

We examined differences in early-life stress and prenatal drug exposure between children who did and did not have RSA data at age 3 years. There were 646 (46.6%) children with missing RSA data at 3 years. One-way analyses of variance (ANOVAs) revealed that children with missing RSA data had caregivers with fewer depressive symptoms, F (1, 1,050) = 4.41, $p = .04$, and were more likely to have an open CPS case between the ages of birth to 1 year, F (1, 1,379) = 9.84, $p = .002$. We conducted the same analyses between children with and without externalizing and internalizing data at 3 years and found that children with missing data were more likely to come from lower SES families as measured by the ISP, F (1, 1,363) = 4.29, $p = .04$, and were more likely to have had an open CPS case between the ages of birth to 1 year, F (1, 1,379) = 5.26, $p = .02$. We also examined demographic differences between children with and without missing outcome data at 3 years and found no differences in birth weight, sex, or site between children with and without missing outcome data.

Results

Descriptive Statistics

Table 2 includes means, *SD*s, and correlations among all variables. There were strong positive correlations between SES variables, and moderate positive correlations between the SES variables and maternal symptoms of depression, psychiatric symptoms, and parenting stress. There were also strong positive correlations between maternal symptoms of depression, psychiatric symptoms, parenting stress, and caregiver history of abuse. Postnatal substance use by the caregiver was correlated positively with having less than a high school education, having a lower income, and experiencing greater symptoms of depression, psychiatric symptoms, and parenting stress. Children with an open CPS case were more likely to have a caregiver with less education, and more likely to have their current caregiver who used alcohol and marijuana. Higher levels of

Table 3. *Exploratory factor analysis summary*

Variable	Caregiving stress	Economic stress	Postnatal substance use
Index of social position		.77	
High school education		.80	
Poverty status		.61	
Caregiver symptoms of depression	.87		
Caregiver psychological distress	.88		
Parenting stress	.66		
Caregiver victimization	.54		
Caregiver postnatal tobacco use			.69
Caregiver postnatal alcohol use			.70
Caregiver postnatal marijuana use			.55
Eigenvalue	2.65	1.44	1.27
% Variance explained	26.45	14.39	12.72

Note. Factor loadings with a weight of $\geq .40$ are reported; socioeconomic status variables (index of social position, high school education, and income) are reverse-scored such that higher levels of these variables indicate having a lower index of social position, lower income, and are less likely to have a high school education, $n = 512$.

prenatal drug exposure were related to a lower index of social position, a caregiver having received less than a high school education, lower income, a caregiver history of abuse, and caregiver postnatal substance use. These children were more likely to have an open CPS case. Greater internalizing and externalizing behavior at age 3 years was associated with lower SES as indexed by the ISP, parent education, and income. It was also related to greater caregiver-reported psychological distress, as indexed by symptoms of depression, psychiatric symptoms, and parenting stress. These children were also more likely to be prenatally drug exposed. Greater resting RSA at age 3 years was related to fewer caregiver symptoms of depression, fewer caregiver psychiatric symptoms, and greater prenatal substance exposure.

Preliminary Analyses

Given moderate-to-strong correlations between variables measuring various forms of stress the child experienced between birth to 1 year, we conducted exploratory and confirmatory factor analyses to determine whether variables could be grouped into dissociable factors. Although the social position variable was comprised both of income and education, we included two dichotomous variables (poverty status and education) because they may identify children in the sample who are at the extremes of low education and poverty. First, after randomly selecting half of the sample, exploratory factor analysis (EFA) was conducted with an oblimin rotation on the 12 stress variables. The EFA produced a three-factor solution. Associated eigenvalues accounted for 53.6% of the variance in variable scores (Table 3). Cross-validation on the second half of the sample was conducted using confirmatory factor analysis (CFA). This suggested excellent stability of item loading (see Figure 1). The EFA and CFA revealed three factors, including (i) a "caregiving stress" factor, comprised of symptoms of depression, psychiatric symptoms, parenting stress, and caregiver history of abuse; (ii) an "economic stress" factor, comprised of the ISP, high school education, and income variables; and (iii) a "drug exposure" factor, comprised of caregiver postnatal use of alcohol, tobacco, and marijuana. Child CPS involvement and postnatal cocaine exposure did not load well on any one factor and were therefore included as individual predictors in subsequent models.

We controlled for False Discovery among the eight tests of interaction using the Benjamini and Hochberg (1995) procedure. This method was used to determine the percentage of findings that could be a false discovery. Instead of a corrected p value, a q value is obtained, which represents the proportion of tests below, which are false positives. We chose a q value of .10. In the Results section, we present both the p value and q values.

Covariates

Covariates tested included birth weight, race, site, and sex. Birth weight was not related to RSA at age 1 month, age 3 years, or to

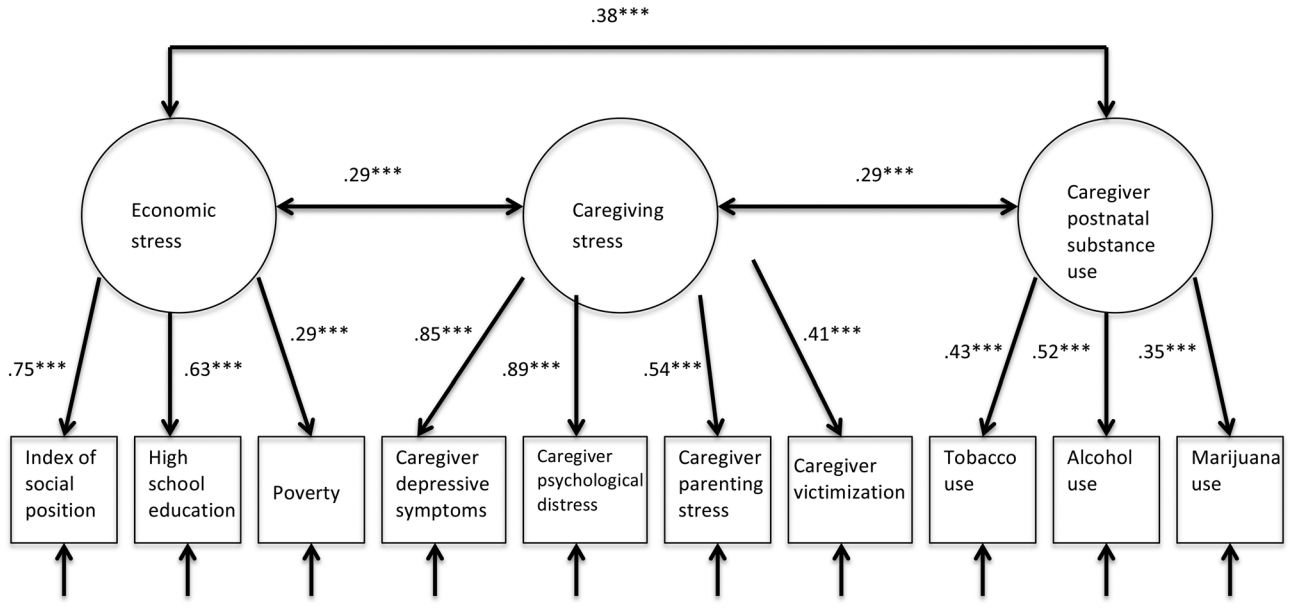

Figure 1. Confirmatory factor analysis of stressors experienced during the first year of life. Paths are standardized beta coefficients. χ^2 (39) = 133.59, $p < .001$; Comparative fit index (CFI) = .96; Standardized root mean square residual (SMSR) = .04, $n = 694$, ***$p < .001$.

Table 4. *Unstandardized parameter estimates and standard errors for predicting behavior dysregulation and baseline respiratory sinus arrhythmia (RSA) at age 3 years*

	Behavior Dysregulation ($n = 827$)		Resting RSA in African Americans ($n = 802$)	
Predictor	*B*	*SE*	*B*	*SE*
Site	—	—	.08**	.03
Race	−2.10**	.77	—	—
Sex	—	—	0.18	0.12
Economic stress factor	10.12	6.35	−1.70	1.52
Caregiving stress factor	36.77***	7.23	−2.19*	1.08
Postnatal substance exposure factor	20.33	15.61	−7.68*	3.74
Child Protective Services involvement	5.24***	1.33	−0.22	0.20
Prenatal drug exposure	–.24	0.35	0.03	0.05
Postnatal cocaine exposure	−2.31	2.68	0.09	0.35
RSA reactivity at 1 month	−0.48	0.47	0.17	0.09
RSA Reactivity × Caregiving stress	−17.86**	7.07	−2.37*	1.18

Note. Standard error and parameter estimates come from a structural equation model.
*$p < .05$. **$p < .01$. ***$p < .001$.

internalizing or externalizing behavior, all *p*s > .32. Sex was related to resting RSA at age 3 years, with females exhibiting greater resting RSA than males, F (1, 734) = 4.67, $p = .03$. A one-way ANOVA revealed site differences in RSA reactivity at age 1 month, with newborns in Providence exhibiting greater RSA reactivity than newborns in Detroit. There were also site differences in internalizing and externalizing behavior, with preschoolers in Detroit exhibiting significantly higher internalizing and externalizing behavior compared to preschoolers in Miami and Providence, and preschoolers in Memphis exhibiting significantly higher externalizing behavior than preschoolers in Miami. There was no main effect of site on resting RSA at 3 years, but when included in full models, significant site effects emerged for African Americans. We therefore include site as a covariate in models predicting resting RSA at 3 years. Race was related to internalizing behavior, with African Americans exhibiting greater internalizing behavior compared to Caucasians. There was a main effect of race on resting RSA at 3 years, with African Americans exhibiting significantly higher resting RSA than non–African Americans, F (1, 733) = 22.03, $p < .001$. We therefore included site and race (dichotomized as African American vs. non–African American) as a covariate in all models. Given that children with prenatal cocaine exposure were oversampled, we also included prenatal substance exposure as a covariate in all analyses.

Structural Equation Models

Behavior dysregulation at 3 years. Predictors of behavior dysregulation (latent variable comprised of internalizing and externalizing behavior) included site, race, caregiving stress, economic stress, postnatal drug use stress, CPS involvement, and RSA reactivity at 1 month. Interactions between RSA reactivity at 1 month and our four stress variables (economic stress, caregiving stress, postnatal drug exposure, and child CPS involvement) were run in separate models. We only include models with a significant interaction term, but output from other models is available from the first author upon request. As shown in Table 4, greater caregiving stress and CPS involvement experienced between birth and 1 year predicted greater behavior dysregulation at age 3 years. There was no main effect of RSA reactivity at age 1 month on behavior dysregulation at age 3 years, although RSA reactivity did interact with caregiving stress to predict behavior dysregulation (Figure 2a). To clarify the nature of this interaction, we examined RSA reactivity and caregiving stress at 1 *SD* above and below the mean using online computational tools provided by Preacher, Current, and Bauer (2006) (http://www.quantpsy.org/interact/mlr2.htm; Preacher). On average, there were no significant associations between RSA reactivity at 1 month and behavior dysregulation at age 3, nor was there a significant association between RSA reactivity and behavior dysregulation among infants with low levels of caregiving stress exposure. However, among infants with high levels of caregiving stress exposure, greater RSA withdrawal was related to elevated symptoms of behavior dysregulation.

Resting RSA at age 3 years.[1] We repeated the analyses described above with resting RSA as our outcome. When race was included in the models, there was a main effect of caregiving stress on resting RSA at 3 years, with greater caregiving stress experienced from birth to 1 year being associated with lower resting RSA at 3 years ($b = -2.01$, $p = .04$, $q = .03$). However, this main effect was qualified by a significant Caregiving Stress × RSA Reactivity × Race interaction. As shown in Table 4, among African Americans only, greater postnatal drug exposure and greater caregiving stress experienced between birth and age 1 year was related to lower resting RSA at age 3 years. This main effect of caregiving stress, however, was qualified by a significant interaction between caregiving stress and RSA reactivity at age 1 month (Figure 2b). Respiratory sinus arrhythmia and caregiving stress were again probed at 1 *SD* above and below the mean. Among children who experienced high levels of caregiver stress, there was no relation between RSA reactivity at 1 month and resting RSA at 3 years. However, lower levels of RSA reactivity at 1 month were related to higher resting RSA at 3 years, but only among children who experienced low levels of caregiver stress. There were no significant interactions between RSA reactivity at 1 month and the other stress variables (economic stress, postnatal drug exposure, or child CPS involvement). These same models were tested with non–African Americans only. No significant main effects or interactions were found.

Discussion

We examined effects of SES and associated stressors, and Stress × RSA Reactivity interactions during the first year of life to identify predictors of behavior dysregulation and resting RSA at age 3 years. Our findings highlight the importance of studying how stressors associated with low SES can shed light on how individual differences in physiological reactivity associate with behavioral and physiological outcomes. Our factor analytic approach revealed three dissociable, or distinguishable, early-life stress factors, one of which interacted with RSA reactivity to predict behavior dysregulation in the sample as a whole, and resting RSA among African Americans. The false discovery rates were low, indicating that our results likely represent true discoveries. Below we speculate on

1. There was a significant positive correlation between resting RSA at 1 month and resting RSA at 3 years ($r = .10$, $p = .02$, $n = 575$). Resting RSA at 1 month is not included as a predictor or potential moderator in our analyses as our interest was in how stress reactivity may interact with environmental conditions to predict behavior and physiological outcomes, per allostatic load and ACM theories.

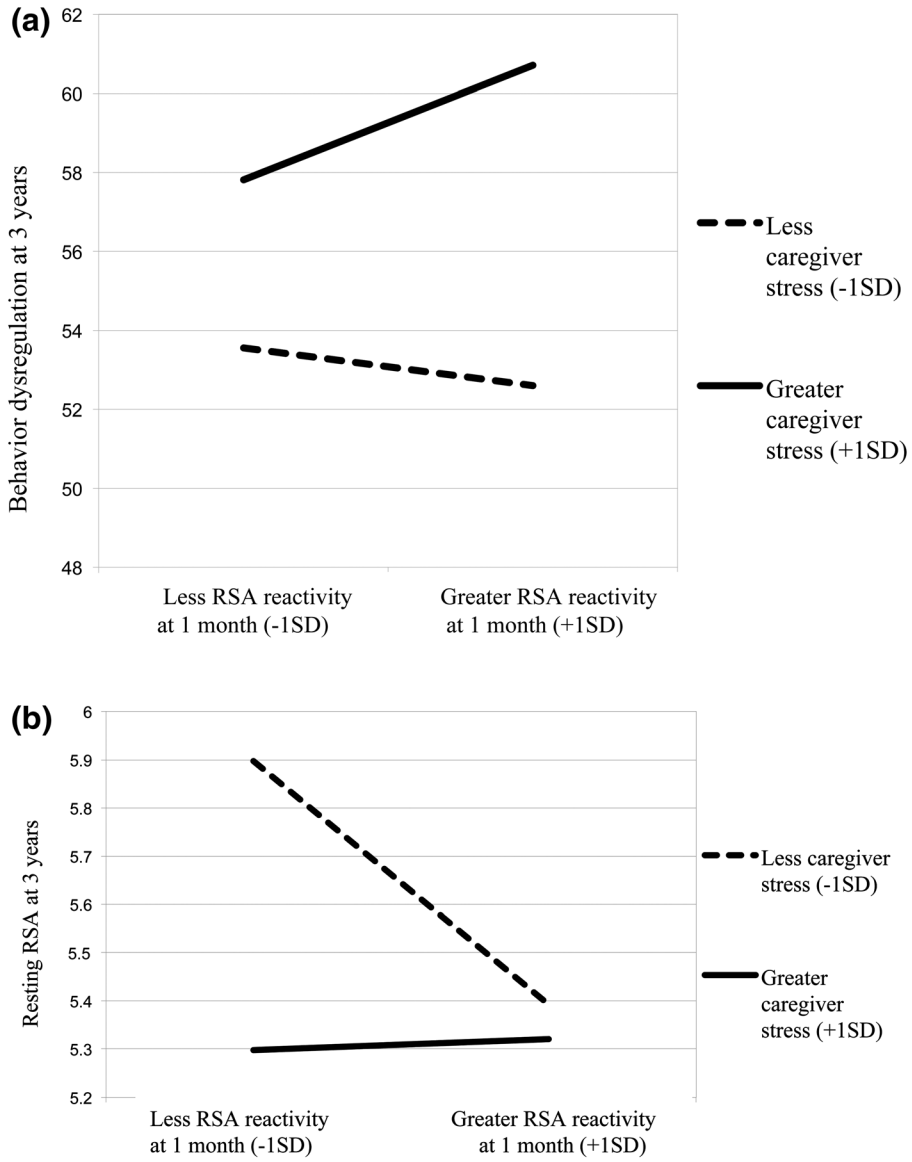

Figure 2. Respiratory sinus arrhythmia (RSA) reactivity at one month × caregiving stress exposure (birth – 1 year) predicts behavior dysregulation at age 3, ($n = 827$) (a), and resting RSA at 3 years in African Americans ($n = 802$) (b). Simple slopes were tested at ± 1SD above and below the mean of RSA reactivity and caregiving stress.

potential mechanisms that may underlie these effects, and broaden discussion of the importance of testing current theories of physiology–behavior relations among populations who are heterogeneous vis-à-vis SES.

First, in this article we expand on the early-life stress literature by studying how multiple types of stressors experienced during the first year of life affect physiology–behavior relations. Three dissociable factors emerged from both EFA and CFA approaches: an economic stress factor, a caregiving stress factor, and a postnatal drug exposure factor. The caregiving stress factor interacted consistently with RSA reactivity at age 1 month to predict problem behavior and resting RSA at age 3 years. There is a large literature supporting the premise that caregivers affect and are affected by infant responses to stress during the first year of life (Conradt & Ablow, 2010; Moore & Calkins, 2004). It is therefore less surprising that the caregiving factor was more closely associated with infant physiological function at 1 month than the other factors (Propper, 2013). Exposure to caregiving stress is more proximal than economic stress or postnatal drug exposure, the effects of which may not emerge until later in life (Shonkoff, Boyce, & McEwen, 2009). Furthermore, we may have hit a floor effect with our economic stress factor, given that the majority of children in our sample were raised in low-SES environments. Given that all three factors were significantly and positively correlated, however, economic and postnatal substance exposure may have exerted an indirect effect through caregiving stress to predict outcomes, a possibility to be explored in future studies.

Our results extend prior research by demonstrating that RSA reactivity at 1 month of life predicts behavior dysregulation at age 3, but only among infants with exposure to high levels of caregiving stress. These results suggest that infants who are more reactive at age 1 month may be more sensitive to an environment characterized by caregiver depression, psychological distress, and parenting stress. When confronted by maternal unavailability, a child's autonomic reactivity may be coupled with increased behavioral

reactivity/frustration, which is adaptive in this context because it signals to the caregiver the child's need for attention. Over time, however, heightened behavioral and physiological reactivity may downregulate the stress response system, thereby reducing the child's sensitivity to negative environments, which may in turn promote disruptive behavior (see Beauchaine et al., 2011; Del Giudice et al., 2011). Our findings are also in support of biological sensitivity to context theory (Boyce & Ellis, 2005). The most reactive infants appeared to be the ones who were more sensitive to caregiving stress, given that caregiving stress was related to behavior dysregulation among these infants, but not among infants who were less reactive. This work also supports current theorizing that stress experienced early in life may affect physiological systems involved in self-regulation, given that high-reactive infants exhibited more behavior dysregulation (indicative of poor self-regulation), but only if caregiving stress exposure was high (Evans & Kim, 2013). These results are important because they suggest that we may be able to identify which children are more sensitive to environmental adversity by age 1 month.

We then examined whether high-reactive infants may exhibit low resting RSA at age 3, given current theorizing that chronic activation of the stress response system may manifest in changes to baseline physiology, presumably through lowered resting RSA (El-Sheikh & Hinnant, 2011). Across numerous samples spanning developmental epochs from infancy to adulthood, high resting RSA is associated with positive mental health outcomes, including better self and emotion regulation, greater social competence, and empathic responding to others who are in distress (see Beauchaine, 2001, 2015). We found a significant interaction between caregiving stress exposure and RSA reactivity at 1 month, but only for African Americans. Among African Americans, infants who were more physiologically reactive at 1 month had the lowest levels of resting RSA, regardless of their level of caregiving stress exposure. However, children with less RSA reactivity at age 1 month had the highest resting RSA if raised in contexts of low caregiving stress exposure, but low resting RSA if raised in contexts of high caregiving stress exposure. These results were surprising. We expected, based on theory and prior work (El-Sheikh & Hinnant, 2011), that greater RSA reactivity in infancy combined with greater stress exposure would predict lower resting RSA. However, our results are not incongruent with current theory. This finding supports the allostatic load model as it suggests that increased RSA reactivity, presumably experienced during the first 3 years of life, comes at a "cost" in the form of lower resting RSA at age 3, a possible vulnerability for poor social competence and emotion dysregulation (Beauchaine, 2001, 2015; Beauchaine et al., 2007). In other words, lower resting RSA among infants with greater caregiving stress exposure may be a result of downregulation of the stress response system (El-Sheikh & Hinnant, 2011; McEwen & Stellar, 1993). The highest resting RSA was observed among less reactive infants, but only if they experienced lower levels of caregiving stress. These results are more consistent with what is found in the literature with typically developing children. If stress physiology systems are not being used chronically, as expected among infants raised by caregivers who are less stressed and without psychopathology, then resting RSA should be higher compared to infants with high caregiving stress exposure, which suggests increased social competence and emotion regulation (Beauchaine, 2001, 2015; Beauchaine et al., 2007). Less caregiving stress exposure may therefore be conceptualized as protective in this group of infants.

It is unclear why the interactive effects of caregiving stress and RSA reactivity at 1 month were found to predict resting RSA only for African Americans. There were no significant differences in caregiving stress exposure between African Americans and non–African Americans in this sample, nor were there differences in RSA reactivity at 1 month. Differences in the developmental trajectory have been found between African Americans and European Americans, with African Americans exhibiting greater baseline RSA at age 8 (El-Sheikh, Hinnant, & Erath, 2011), that remained stable across middle childhood (Hinnant, Elmore-Staton, & El-Sheikh, 2010). Given that differences in RSA emerged between 1 month and 3 years in this sample, there may be an unexplored third variable that accounts for differences in the autonomic nervous system between racial groups, such as parental experience of stereotype threat or perceived racism (Lepore et al., 2006). Alternatively, we may have had increased power to detect this moderation effect, given that African Americans represented the majority of this sample.

These results also support a fetal programming model, which helps to explain why an infant would exhibit high RSA reactivity, a presumed risk factor for adverse behavioral and physical health outcomes. In brief, the concept of programming is based on epidemiological studies suggesting that an adverse fetal environment resulting in low birth weight in term infants was associated with the development many decades later of adult cardiovascular and metabolic disorders (Barker, 1998; Barker & Osmund, 1986). This was attributed to fetal adjustments to cues from the intrauterine environment (programming) that increased disease susceptibility in adulthood (Entringer, Buss, & Wadhwa, 2010; Sandman, 2015). Infants who were more reactive may have been "preparing," based on pregnancy conditions such as prenatal drug exposure, to enter into a more unpredictable, stressful postnatal environment. Prenatal stress exposure may also impair prefrontal cortex development (Kishiyama et al., 2008) which is known to exert downstream consequences on RSA reactivity (Beauchaine, 2015). Postnatal programming by insensitive or unresponsive caregiving behavior could in turn affect prefrontal cortex development and stress physiology (Meaney, Szyf, & Seckl, 2007). This heightened reactivity may be adaptive in this setting as it facilitates attunement and sensitivity to changes in the environment (Boyce & Ellis, 2005; Sandman, 2015). By age 3, however, increased reactivity may come at a cost, as infants with the greatest RSA reactivity had the highest behavior dysregulation, and lowest resting RSA if also raised in environments of high caregiving stress.

Implications

Our results highlight the importance of examining low SES and associated stressors in psychophysiological research, as what we know about psychophysiological processes in typically developing children may not necessarily apply among low-income populations. In the past, particularly in research on prenatal substance exposure, SES was viewed as a confound that needed to be controlled for in order to test direct effects of a substance on behavioral and physiological outcomes. More recently, research suggests that prenatal substance exposure may be more of a marker of the quality of the postnatal environment (Fisher et al., 2011), and that meaningful relations between SES and physiological outcomes are obscured when SES is ignored (Conradt et al., 2013; Fisher et al., 2011). For example, although there was a main effect of caregiving stress on physiological and behavioral outcomes, this effect was qualified by a significant interaction between caregiving stress and RSA reactivity. Thus, this research suggests that effects of stressors associated with low-SES environments on behavior dysregulation may be magnified among children with high RSA reactivity, whereas

effects of stress on resting RSA are stronger for children with low RSA reactivity.

One reason why SES is often ignored is because until recently, there have been few theoretical models that imply Physiology × Environment interactions. Allostatic load and adaptive calibration models usher in a resurgence of interest in how SES may affect psychophysiological functioning. Nevertheless, our findings highlight a number of research questions left to be answered. One of the most difficult is how to characterize a child as exhibiting "high," "medium," or "low" reactivity (Obradović, 2012). In addition, in order to fully test these models, one must also include of a range of children from high-, medium-, and lower stress backgrounds, all of whom have been assessed at similar ages using similar psychophysiological methods and protocols. One of the limitations of the current study is that the sample is primarily low SES. It is therefore difficult to determine what constitutes "high," "medium," and "low" RSA reactivity, because low reactivity in a child raised in a low-SES context may actual exhibit high RSA reactivity when compared against a child who comes from a middle-class family with fewer stress exposures (Gatzke-Kopp, Greenberg, & Bierman, 2015). Researchers who pool together data from multiple samples, assessed using similar physiological methods, may be able to overcome this limitation.

Additional key unanswered questions include how particular stressors, experienced by particular children, of particular duration, during a particular developmental epoch, affect psychophysiological processes. With regard to the stressors that are most pernicious, this answer probably depends on the developmental period in question. Our results indicate that caregiving- related stress that may affect psychophysiological outcomes, at least in early childhood. Our work, along with that by others, indicates that children who are most sensitive to adverse environments are also the most reactive, although as mentioned previously, reactivity is a relative, sample-dependent term. Research suggests there is instability in physiological reactivity, but it is not clear whether children shift from "high" to "low" reactivity (or vice versa) because of particular stressors experienced at specific points in time (Bornstein & Suess, 2000). The adaptive calibration model suggests that there are multiple "switch points," or sensitive periods, though these periods appear to span the entirety of childhood (Del Giudice et al., 2011). Again, large, representative longitudinal data sets pooled across research teams are needed to best answer these questions.

Key in answering questions related to what constitutes "high," "medium," or "low" reactivity are valid assessments of SES. We measured SES status using a latent factor comprised of whether or not the primary caregiver completed high school, the primary caregiver's income, and the Hollingshead ISP (e.g., occupation). This is an efficient method of collecting SES that is consistent with other approaches used in the developmental and psychophysiological literature. However, there is also a subjective measure of SES that may provide novel insights into SES x physiology relations, as it may be reflective of how one's perceived social standing affects daily cognitive and emotional processing of perceived threats, at least in adults. The MacArthur Scale of Subjective Social Status (e.g., the MacArthur "ladder") assesses one's perception of their social status on traditional SES indicators (e.g., education and income; Adler, Epel, Castellazzo, & Ickovics, 2000), as well as their standing in the community. A parent's perceived SES may be related to child health outcomes as well, as perceived SES may affect parental mood and subsequent parent–child interactions. Use of this scale may add to our understanding of how the experiences of adults living in low-SES contexts impact physiology and physical health outcomes (Adler et al., 2000).

Our results are consistent with studies of typically developing children that find that, in conditions of high versus low levels of stress or adversity, greater RSA reactivity is related to poor psychosocial outcomes (e.g., Obradović et al., 2010). Yet there are exceptions. Hastings and colleagues (2008) found that the highest internalizing problems among preschoolers (ages 2–4 years) were exhibited by those who demonstrated less vagal withdrawal to emotional challenge and had fathers who were less supportive, whereas others have found that low RSA withdrawal at 6 months is related to stable, high levels of fear in early childhood (Brooker et al., 2013). In relation to predictors of resting RSA, we are finding that greater RSA withdrawal is related to poor behavioral outcomes in high-stress contexts. Similar findings have been reported by others in middle childhood. For example, boys who demonstrate greater RSA withdrawal and are exposed to marital conflict show decreasing resting RSA across time (El-Sheikh & Hinnant, 2011). These results are probably not due to differences in resting RSA in preschool in our sample as our measure of resting RSA at age 3 was only slightly lower compared to other studies with typically developing 2- to 5-year-old children (Alkon et al., 2003; Alkon et al., 2011; Calkins & Keane, 2004).

Our findings may also have implications for understanding the relative contribution of early-life stress and prenatal substance exposure on biobehavioral outcomes in early childhood. Whereas most children in this sample were exposed to at least one substance prenatally, there were no main effects of prenatal substance exposure on behavior dysregulation or resting RSA at age 3. Effects of prenatal drug exposure on biobehavioral outcomes, while subtle, may occur through the quality of the postnatal caregiving environment (Conradt et al., 2013; Fisher et al., 2011). Research with this sample, for instance, indicates that early-life stress measured using a cumulative-risk approach mediates the relation between prenatal drug exposure and development of RSA across early childhood (Conradt et al., 2013). Such findings point to the importance of intervening at the level of the caregiving environment by lowering parental stress and depression, particularly among infants with prenatal substance exposure who are more physiologically reactive.

Limitations and Conclusions

It is important to note that without random assignment, we cannot infer causality in links between our independent and dependent variables. However, recent intervention research indicates clear associations between environmental risk exposure, including changes in parenting, and alterations in children's psychophysiological functioning (e.g., Beauchaine et al., 2015). Future research would benefit from additional intervention studies, which can provide evidence that caregiving behavior has a stronger effect on problem behavior among infants with specific physiological profiles (Beauchaine et al., 2013, 2008). We also used only one measure of physiology, RSA (both at rest and in response to a mild stressor). Including sympathetic and neuroendocrine markers of stress could help to uncover additional pathways through which early-life stress is related to physiological and behavioral outcomes. There was also a high percentage of missing RSA data at age 3. The high number of missing data was due to lack of clarity around the importance of including a baseline measurement across sites. Site was included as a covariate in analyses for

resting RSA, though the number of missing resting RSA data at age 3 is still of concern. Another limitation includes our measurement of resting RSA. We did not assess RSA while children were truly at "rest." Children were allowed to move and engage in some attention deployment before the attention-demanding task. Although our estimates of resting RSA converge with other studies, we nonetheless note that our resting measurement did not measure parasympathetic activity at rest and allowing the child to move may limit the internal validity of our findings.

Effects of RSA reactivity on future behavior dysregulation and RSA were different depending on the infant's level of exposure to caregiving stress during the first year of life. Our work is consistent with the adaptive calibration model and biological sensitivity to context theory, and introduces new questions related to how this model may operate to predict behavioral and physiological outcomes in low-SES populations. Much more work is needed to determine for whom specific stressors are most likely to affect behavioral and physiological functioning in resource poor environments. We hope that with renewed focus on how SES can affect health, we may be able to eventually identify children most at risk for poor health outcomes, particularly in this underserved population.

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