

Cortisol Reactivity to Social Stress as a Mediator of Early Adversity on Risk and Adaptive Outcomes

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Children chronically exposed to stress early in life are at increased risk for maladaptive outcomes, though the physiological mechanisms driving these effects are unknown. Cortisol reactivity was tested as a mediator of the relation between prenatal substance exposure and/or early adversity on adaptive and maladaptive outcomes. Data were drawn from a prospective longitudinal study of prenatal substance exposure ($N = 860$). Cortisol reactivity was assessed at age 11. Among African Americans, prenatal substance exposure exerted an indirect effect through early adversity and cortisol reactivity to predict externalizing behavior, delinquency, and a positive student–teacher relationship at age 11. Decreased cortisol reactivity was related to maladaptive outcomes, and increased cortisol reactivity predicted better executive functioning and a more positive student–teacher relationship.

The long-term effects of exposure to adversity early in life are of great interest to psychological scientists. Children exposed to adversity in early childhood in the form of prenatal substance exposure, poverty, maternal depression, and frequent marital conflict are more likely to exhibit externalizing psychopathology, delinquency, and problems with executive

functioning (Blair, Granger, & Peters Razza, 2005; Fisher et al., 2011), all of which make up the spectrum of neurobehavioral disinhibition (Iacono, Carlson, Taylor, Elkins, & McGue, 1999; Tarter et al., 2003). We have previously reported that early postnatal adversity mediates the relation between prenatal substance exposure and neurobehavioral disinhibition in adolescence (Fisher et al., 2011). Unclear at this point is how this process occurs. The theory of allostatic load suggests that early adversity becomes biologically embedded to affect stress response systems, which in turn impact the development of psychopathology (McEwen, 1998). In this study, we test whether the effects of early adversity on the components of neurobehavioral disinhibition (externalizing behavior and delinquency) are mediated by the neuroendocrine response as

This study was supported by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network and an interinstitute agreement with the National Institute on Drug Abuse (NIDA) through cooperative agreements: U10-DA-024117-01, U10-HD-21385 (to S. S.), I10-DA-024128-06, U10-HD-2786 (to H. S. B.), U10-DA-024119-01, U10-HD-27904 (to B. M. L.), and U10-DA-024118-01, U10-HD-21397 (to C. R. B.); NICHD Contract N01-HD-2-3159 (to B. M. L.); and a National Research Service Award from the National Institute on Drug Abuse F32DA032175 (to E. C.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse, the National Institute of Child Health and Human Development, or the National Institutes of Health.

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DOI: 10.1111/cdev.12316

measured by cortisol. Far less attention has been paid to studying positive outcomes among children with prenatal substance exposure and thus we also investigate whether neuroendocrine functioning mediates the effects of early adversity on executive functioning and a positive student–teacher relationship.

Children confronted with unpredictable, threatening, and repeated stressors are more likely to exhibit alterations in glucocorticoid hormones such as cortisol (Mills-Koonce, 2012). Cortisol is one of the hormonal products of the limbic–hypothalamic–pituitary–adrenocortical (LHPA) system. In response to stress, brain regions in the limbic system (e.g., hypothalamus, amygdala, and hippocampus) stimulate the release of corticotropin-releasing factor (CRF). CRF then activates the pituitary gland to release adrenocorticotrophic hormone (ACTH) into the bloodstream, which in turn stimulates cells in the adrenal glands to produce cortisol, which is also released into the bloodstream (Gunnar & Vazquez, 2006; Stansbury & Gunnar, 1994). High levels of cortisol stimulate a negative feedback loop that inhibits the release of CRF and ACTH, which results in a decrease of cortisol to baseline levels (Gunnar & Vazquez, 2006). In response to acute stress or challenge, the LHPA axis is activated, triggering the release of glucocorticoids that facilitate the “fight or flight” response (Gunnar & Vazquez, 2006; Susman, 2006). In the short term, increases in cortisol allow for selective memory enhancement and increases in alertness (Susman, 2006). According to the theory of allostatic load, however, repeated activation of the LHPA system may “cost” the system in the form of “wear and tear” on the body, subsequently increasing the likelihood of disease (Juster et al., 2011; McEwen, 1998) and psychopathology (McEwen, 2003).

In this study, we examined two indices of adversity: (a) a summative index of prenatal substance exposure and (b) a cumulative risk index of stressful events experienced early in life, termed *early adversity*. Prenatal exposure to substances such as cocaine, alcohol, tobacco, marijuana, and opiates is a known teratogen. Although each mechanism of action is different, all have documented harmful effects on the developing fetus and fetal brain development (O’Rahilly & Müller, 2001). Emerging evidence suggests that exposure to different types of drugs is a good indicator of cumulative stress (Hellemans, Sliwowska, Verma, & Weinberg, 2010; Lester & Padbury, 2009). In the case of cocaine, Lester and Padbury (2009) have argued that cocaine alters the expression of key candidate genes and gene networks important to placental function in late gestation. Specifically, reduced expression of the norepinephrine transporter gene in the placenta,

which regulates the amount of cortisol to which the fetus is exposed, has been found among mothers who took cocaine and nicotine in utero (Kumar et al., 2005; Lester & Padbury, 2009). A similar process is thought to occur in response to prenatal alcohol (Hellemans et al., 2010) and tobacco (Knopik, Maccani, Francazio, & McGeary, 2012) exposure. Thus, we argue that the exposure to multiple substances, rather than a single substance per se, may make it more likely that the fetus is exposed to higher levels of maternal cortisol.

Early adverse experiences among children with prenatal substance exposure tend to co-occur and include exposure to parental psychopathology, neighborhood violence, chaotic home environments, and lack of monetary resources (Dong et al., 2004; Propper, 2012), making it extremely difficult to separate the effect of one adverse experience from the other. Cumulative risk models have been shown to be a more powerful predictor of problem behavior among children with prenatal substance exposure than risks examined in isolation (Ghosh Ippen, Harris, Van Horn, & Lieberman, 2011). Exposure to these adversities early in life is likely to disrupt the neuroendocrine system. These changes may manifest as a *hypercortisolism* or a *hypocortisolism* response to stress (Davies, Sturge-Apple, Cicchetti, & Cummings, 2007). The hypercortisolism hypothesis suggests that repeated exposure to early adversity may sensitize the LHPA axis to stress in the form of hyperactivity of the LHPA axis. The hypocortisolism hypothesis posits that children who experience repeated stressors may exhibit a diminished or dampened response to stress (Davies et al., 2007). This response is more common among children exposed to significant, repeated stressors early in life, such as children in foster care (Fisher, Gunnar, Dozier, Bruce, & Pears, 2006), children with both prenatal substance exposure and postnatal exposure to domestic violence (Lester et al., 2010), and children with abuse histories (for a review, see Mills-Koonce, 2012). Children with prenatal substance exposure in particular may be more likely to exhibit a hypocortisolism response (Moss, Vanyukov, Yao, & Kirillova, 1999), lower basal cortisol (Jacobson, Bihun, & Chiodo, 1999), and an absence of cortisol reactivity to stress (Magnano, Gardner, & Karmel, 1992), though there are exceptions (Eiden, Veira, & Granger, 2009). We therefore expect to see a hypocortisolism response in our sample due to the high rates of prenatal substance exposure and exposure to early adversity.

Cortisol dysregulation may then in turn mediate the effect of early adversity on problem behavior. Susman’s (2006) *attenuation hypothesis* suggests that

biological vulnerabilities, including those resulting from prenatal substance exposure and/or exposure to an adverse environment, results in attenuation of the stress response system (i.e., hypocortisolism), exacerbating risk for psychopathology. In other words, the stress system should mediate the relation between early vulnerabilities and poor behavioral outcomes. In partial support of the attenuation hypothesis, Davies et al. (2007) found that interparental conflict was associated with less cortisol reactivity in kindergarteners, and this dampened reactivity was in turn associated with increases in externalizing behavior across a 2-year period. On the other hand, there are two published studies that have found null results when examining cortisol reactivity as a mediator of early life experiences on aggression in adolescence (Marsman, Rosmalen, Oldehinkel, Ormel, & Buitelaar, 2009; Ryan, Schechter, & Brennan, 2012). However, these studies examined the influence of one risk factor during the perinatal period (i.e., obstetric complications or minor physical anomalies in the fetus as a measure of prenatal risk). Consistent with the theory of allostatic load, in this study we take a cumulative risk approach to studying how a multitude of stressors impact deviant behavior and psychopathology. We also examine positive outcomes of relevance in adolescence: executive functioning and a positive student–teacher relationship.

Less is known about associations between *hyper-* and *hypocortisolism* and executive functioning. The neuroendocrine response to stress may be related to problems with executive functioning because stress hormones modulate synaptic activity in the prefrontal cortex (Blair et al., 2005), the “site” for executive functions including inhibitory control, working memory, and shifting between task demands. Among children reared in poverty, a pattern of cortisol reactivity characterized by moderate increases in response to stress, followed by a decrease, was associated with better executive functioning (Blair et al., 2005). We also focus on predictors of a positive student–teacher relationship because the quality of this relationship may be related to how a child responds and recovers from stress. A child who can flexibly respond physiologically to stress may be better regulated and socially competent. This type of response may be related to the ability to maintain positive, supportive relationships with adults, including teachers. For instance, among preschoolers, the ability to manifest a moderate cortisol response to mild stress was associated with better self-regulation and executive functioning (Blair et al., 2005). Students with elevated cortisol levels

across the school week experienced more conflict with their teachers (Ahnert, Harwardt-Heinecke, Kappler, Eckstein-Madry, & Milatz, 2012). It is important to identify the precise physiological mechanisms that may explain how positive outcomes develop among children with prenatal substance exposure so that we can identify specific pathways to competence among these children who are at high risk for poor developmental outcomes.

These pathways may look different depending on a child’s race. A number of studies have documented differences in cortisol functioning among African Americans, Hispanics, and Caucasians. African Americans and Hispanics were observed to have lower levels of the cortisol awakening response compared to Caucasians (Hajat et al., 2010). Two studies found that African Americans also had a flatter diurnal cortisol pattern compared to Caucasians (Hajat et al., 2010; McCallum, Sorocco, & Fritsch, 2006). These effects are at times independent of socioeconomic status (DeSantis et al., 2007) though not always. For instance, Bennett, Merritt, and Wolin (2004) found lower cortisol levels among African American participants with lower levels of education compared to those with higher levels of education. We therefore test for moderation by race in our models.

Current Study

This study provides a direct test of the attenuation hypothesis outlined by Susman (2006), which suggests that biological vulnerabilities including prenatal substance exposure, and/or the experience of early adversity, results in a dampening, or attenuation of the cortisol response to stress. This response in turn is related to externalizing behavior, delinquency, and symptoms of externalizing psychopathology. We expect to find evidence of hypocortisolism because vulnerability in the form of prenatal exposure to stress due to prenatal substance exposure, and exposure to postnatal early adversity, will make it more likely for children to exhibit a dampened cortisol response. The rationale for including the behavioral outcomes is based on the existing literature and data suggesting that these behaviors are accompanied by a dysregulated neuroendocrine response to stress. As the absence of a negative outcome is not the same as a presence of a positive one, we also extend prior work by examining executive functioning and a positive student–teacher relationship, in efforts to better understand contributors to adaptive outcomes in this population. We study cortisol reactivity at age

11 because by this age the effects of early adversity and prenatal substance exposure may have become biologically embedded to impact the LHPA response to stress. Furthermore, problem behavior, particularly externalizing psychopathology and delinquency, is more likely to manifest in adolescence as opposed to childhood.

This study had two major aims. First, we examine the main effects of prenatal substance exposure, early adversity, and cortisol reactivity on the following five outcomes: (a) externalizing behavior, (b) symptoms of externalizing psychopathology, (c) delinquency, (d) executive functioning, and (e) a positive student–teacher relationship. On the basis of theory and prior work, we expected that prenatal substance exposure and early adversity would be related to hypocortisolism. We also expected that hypocortisolism would be related to greater externalizing behavior, symptoms of externalizing psychopathology, and delinquency. On the other hand, less prenatal substance exposure should be related to less exposure to early adversity and, in turn, increases in cortisol. This response should be related to our adaptive outcomes: greater executive functioning and a positive student–teacher relationship. Second, because of our interest in examining mechanisms involved in the development of problem behavior and positive outcomes in adolescence, we tested whether prenatal substance exposure exerts an indirect effect through *both* early adversity and cortisol on these outcomes. Longitudinal studies incorporating measures across behavioral and physiological systems are needed to best model these pathways (Cicchetti & Dawson, 2002). This study is significant as the information gleaned will inform whether: (a) we can use this information to test additional pathways to problem behavior and (b) preventative intervention should begin in early childhood when early adverse experiences may program the LHPA stress system.

Method

Participants

We used data from 1,388 participants drawn from the Maternal Lifestyle Study (MLS), a multisite investigation of the effects of prenatal substance exposure in a longitudinal follow-up from 1 month to 16 years. In this study children were 11 years old ($n = 860$ participants; 421 female). Participants were recruited from Detroit, MI ($n = 377$); Memphis, TN ($n = 228$); Miami, FL ($n = 129$); and Providence, RI ($n = 126$). The MLS sample includes children in the

following racial and ethnic categories: African American (77%), Caucasian (16%), Hispanic (6%), and children whose parents identified other racial or ethnic backgrounds (1%). There were significantly more African American and Hispanic participants in Detroit, and more Caucasians in Providence compared to the other sites, $\chi^2(9) = 299.42$, $p < .001$. Details on the enrollment and exclusion criteria are described elsewhere (Lester et al., 2002). In brief, the 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). The exposed and comparison youths were group matched on race, sex, and gestational age within each study site. Background substances associated with cocaine use (i.e., alcohol, tobacco, and marijuana) were present in both groups; thus, most participants were polysubstance exposed ($n = 178$ unexposed children).

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. Examiners were blind to exposure status.

Measures

Polysubstance Exposure

Because of our conceptualization of prenatal substance exposure as a stressor (Lester & Padbury, 2009), and because polysubstance exposure during pregnancy is the rule rather than the exception (Mayet, Groshkova, Morgan, MacCormack, & Strang, 2008), following the work of Fisher et al. (2011) with this sample, prenatal substance exposure was measured as a summative index ranging from 0 to 5 for use of cocaine, opiates, marijuana, alcohol, and tobacco during pregnancy. Maternal report/meconium screen of drug use (1 = *yes*, 0 = *no*) prenatally was computed. One point was assigned for each substance used ($\alpha = .60$).

Early Adversity

Early adversity was a summative risk index from birth to the age 6 assessment and included nine risk factors. Cumulative risk models (Appleyard,

Egeland, van Dulmen, & Sroufe, 2005; Sameroff, Seifer, Barocas, Zax, & Greenspan, 1987) assume that combinations of risk factors are more powerful predictors of developmental outcomes than the measurement of a single risk factor, which is less ecologically valid in substance-exposed populations (Lester et al., 2005). Each risk factor was either a continuous scale or a count score that was dichotomized to create an overall risk index (0 = *no/none*, 1 = *yes/one or more*).

Maternal Report of Postnatal Substance Use

Any maternal report of postnatal substance use of cocaine, opiates, tobacco, alcohol, or marijuana up to the year 6 assessment was assessed using the Caretaker Inventory of Substance Use (Shankaran et al., 1996). In this study there was 66% agreement between a positive meconium screen for cocaine and maternal report of cocaine use, which is consistent with reports of substance use from individuals who are not currently in drug treatment (Harrison & Hughes, 1997).

Chronic Poverty Status

Chronic poverty status calculated as income below \$10,000 for at least 75% of the visits. Poverty status, or adult self-report of income, is a reliable index of current income among drug users (Johnson, Fisher, & Reynolds, 1999), particularly with regard to test-retest reliability, $r = .82$ (Johnson et al., 1999).

Low Social Status

Low social status was scored from the Hollingshead Index of Social Position (Hollingshead, 1975). Education and occupation were averaged over annual visits. Participants received 1 point if their Index of Social Position score fell 1 *SD* or more below the mean. The Hollingshead Index of Social Position (Hollingshead, 1975) has high internal consistency reliability, range $r = .81-.88$ (Cirino et al., 2002) and was used in developmental research when socioeconomic status was collected with this population in the early 1990s due to its high correlation with developmental outcomes (Gottfried, 1985).

Primary Caretaker Changes

The presence of primary caretaker changes was assessed annually. Primary caretaker changes

assessed using scales that measure changes in recent life events have moderate to high test-retest reliability; $r_s = .56$ to $.88$ (Sarason, Johnson, & Siegel, 1978).

Sexual or Physical Abuse or Neglect

Caregivers were interviewed about whether or not there had been any reports for sexual abuse, physical abuse, and/or neglect annually from the birth to age 6 assessment. Caregivers were asked if there was a report to Child Protective Services (CPS) made on behalf of the study child; if so, the nature of the referral was documented. Caregiver report of sexual or physical abuse has moderate construct validity, test-retest reliability ($\kappa = .56$ for physical abuse, to $\kappa = .56$ for sexual assault, $\kappa = .49$ for child maltreatment, and 100% test-retest agreement when caregivers were asked about whether their child experienced neglect), internal consistency reliability, $\alpha = .80$, and good agreement between child self-report of abuse and caregiver report of child abuse for children under 10 (Finkelhor, Hamby, Ormrod, & Turner, 2005).

Caregiver Depression

Children received 1 point on the cumulative risk index if assessments of caregiver depression were 1 *SD* or greater above the mean for averaged depressive symptoms on the caregiver-reported Beck Depression Inventory (Beck, Steer, & Brown, 1996) at ages 4 months ($\alpha = .88$), 2.5 years ($\alpha = .89$), 4 years ($\alpha = .87$), 4.5 years ($\alpha = .90$), and 5.5 years ($\alpha = .87$).

Caregiver Psychological Distress

This risk item was calculated as present if assessments of caregiver psychological distress were 1 *SD* or greater above the mean for total psychological symptoms on the Brief Symptom Inventory (Derogatis & Coons, 1993) at ages 4 months ($\alpha = .96$), 2.5 years ($\alpha = .96$), and 5.5 years ($\alpha = .97$).

Home Environment

This risk item was coded as present if scores fell 1 *SD* or more below the mean on the Home Observation Measurement of the Environment (Caldwell & Bradley, 1984) as assessed by a home visitor when the child was 10 months ($\alpha = .82$) and 6 years old ($\alpha = .82$).

History of Child Protective Services Involvement

If the child had any history of CPS involvement, assessed annually by caregiver report until the year 6 assessment, then 1 point was given on this risk index. Specifically, 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. CPS involvement as assessed by the caregiver is thought to underestimate the incidence of child maltreatment, as CPS reports include only officially reported cases of maltreatment (Shaffer, Huston, & Egeland, 2008). Although, combined with caregiver report, the number of children identified as having been maltreated increases (Shaffer et al., 2008). Although not corroborated by CPS record review, Hussey et al. (2005) along with others (Leiter & Johnsen, 1994) found no difference in problem behavior among children with substantiated as opposed to unsubstantiated reports of child abuse and neglect. Thus, our measure was a conservative assessment of abuse as we relied on self-report of the caregiver.

Cortisol Reactivity

Cortisol stress reactivity was measured during an expanded version of the Trier Social Stress Test (Kirschbaum, Pirke, & Hellhammer, 1993) at age 11. The Trier Social Stress Test is a standardized protocol for eliciting an acute response to stress among both children and adults. The Trier task lasts a total of 15 min and consists of a 5-min preparation period, followed by a test period in which the participant delivers a speech (5 min) and performs mental arithmetic (5 min) in front of an audience. We added a mirror tracing task (5 min) to provide a challenging nonverbal performance task. The child used a mirror that reversed directionality as they traced the figure of a six-sided star. If the child made an error, the apparatus beeped and the child was instructed to restart the procedure.

Three saliva samples were collected. The prestress sample was collected 20 min before the start of the Trier task and involved children filling out questionnaires on topics that were innocuous and familiar to the child from previous visits (e.g., extracurricular activities, ethnic identity, and a nutrition questionnaire). It took approximately 20 min to fill out these questionnaires. We chose this task before the Trier task because we wanted to control for individual differences in the type of activity the child was engaged in before coming to the laboratory, and to control for

differences in the car ride to the laboratory. The second sample was collected 20 min after the end of the mirror tracing task. During this time, experimenters conducted a debriefing interview with the child, where the research assistants explained the purpose of the tasks and reassured the children that they performed well. The third sample was collected 40 min after the end of the mirror-tracing task.

To collect the samples, the child deposited saliva through a straw directly into a 2-ml vial for each of the three samples. Ideally, the samples were ≥ 1.0 ml but 0.5 ml was accepted if collection time was over 3 min. Samples were immediately placed in a -20°C freezer until shipped on dry ice to Salimetrics Laboratory (Salimetrics LLC, State College, PA) for assay. All samples were assayed in duplicate for salivary cortisol using a highly sensitive cortisol immunoassay kit. Each test uses 25 μl of saliva, has a limit of sensitivity of .007 $\mu\text{g}/\text{dl}$, and a range of sensitivity from .007 to 1.8 $\mu\text{g}/\text{dl}$. Mean intra-assay and interassay coefficients of variations were less than 5% and 10%; averaged duplicate scores were used in all analyses. Ninety-seven percent of participants provided the prestress sample between 11:00 a.m. and 5:00 p.m. to address the diurnal cycle of cortisol that flattens between late morning and early evening. The earliest prestress sample was 10:37 a.m. and the last was 5:10 p.m. We also collected information on steroid medications, time of last meal or beverage including dairy or caffeine, and vigorous physical exercise. Finally, cortisol data as assessed using saliva show excellent reliability. Values from matched serum and saliva samples show a strong, positive, linear relation, $r(63) = .89$, $p < .0001$ (Salimetrics, 2000).

The raw cortisol values ($\mu\text{g}/\text{dl}$) were positively skewed and normalized using a log transformation. Outliers above or below 3 SD in all three samples were winsorized by replacing the value with the value at 3 SD ($< 1.5\%$ of cortisol values were affected).

Outcome Measures

Externalizing Behavior

Externalizing behaviors were assessed using the Child Behavior Checklist (CBCL; Achenbach, 1992), administered to caregivers when children were 11 years old. T scores for externalizing behavior are reported. Caregivers rated whether each of 35 externalizing behavioral symptoms were *not true*, *somewhat/sometimes true*, or *very/often true* over the past 6 months. Thus, we were able to capture the youth's behavioral functioning relative to children

of the same age and sex ($\alpha = .92$ for total externalizing problems).

Symptoms of Externalizing Psychopathology

Parent-reported symptoms of oppositional defiance, conduct disorder, and attention deficit symptom counts from the Diagnostic Interview Schedule for Children–IV (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) were used at age 11. Parents report on whether they have observed specific behaviors within certain time frames by responding to a trained interviewer with “yes” or “no” for most questions. The symptoms were summed and included in the models described next. The coefficient alphas for symptoms of attention deficit hyperactivity disorder, conduct disorder, and oppositional defiant disorder were 0.91, 0.85, and 0.89, respectively.

Executive Function

This score was computed using the spatial working memory and stockings of Cambridge tests from the Cambridge Neuropsychological Test Automated Batteries (Luciana, 2003) at age 11. The spatial working memory task is self-ordered and requires the respondent to find a “token” in an array of colored boxes; we measured the total number of errors on the task. The test–retest reliability for this task ranges from 0.64 to 0.68 (Lowe & Rabbitt, 1998). The Stockings of Cambridge task is a modified version of the Tower of London task and involves spatial planning. The respondents must use “balls” in one display to copy the pattern shown in another display. Thinking time includes two trials measuring the time to select the initial stimulus. Shorter times have been related to impulsivity. We measured the total number of correct solutions in the minimal number of moves. The composite score was the average of the two indicators rescaled to 0–1. We chose tasks that assess spatial working memory, thinking time, and planning, all of which have been shown to be related to brain areas related to deficiencies among children exposed prenatally to drugs (Sclove, 1987).

Delinquency

Delinquency summary scores for the number of child-reported crimes against people and acts of general and school delinquency from the Things That You Have Done Questionnaire (Clausen, Landsverk, Ganger, Chadwick, & Litrownik, 1998) at age 11 were used. Children responded (yes or no) whether they had engaged in delinquent acts

such as hitting another child, stealing, and carrying a weapon ($\alpha = .74$ for total delinquency).

Positive Student–Teacher Relationship

The total number of positive items from the Student–Teacher Relationship Scale–Short Form (Pianta, 2001) was used in this study when children were 11 years old. The 15-item scale assesses the teacher’s relationship with the child. The scale asks teachers to respond to statements on a 1–5 Likert scale about the extent to which the teacher agrees with a number of items assessing the student–teacher relationship, for example, whether the child will seek out the teacher when upset, whether the child responds to praise, and whether the child openly shares his or her feelings with the teacher. Scores ranged from 10 to 40 ($\alpha = .71$).

Missing Data

At age 11, there were 860 children with cortisol data. From the original 1,388 children (assessed 11 years earlier), 388 did not participate in the 11-year visit. One hundred and fifteen children did not participate in the cortisol reactivity task due to chronic disability ($n = 57$), child or parent unable or refusal ($n = 14$), or technical problems or resource limitations ($n = 44$). Of the 885 children who participated in the cortisol reactivity task, 22 had an incomplete procedure or saliva collection, and 3 were excluded because the quantity of saliva was insufficient.

We analyzed whether there were differences in prenatal substance exposure or early adversity among children with and without missing cortisol data. No differences were found in exposure to substances prenatally or exposure to early adversity between children with and without cortisol data (all F s ≤ 2.85 , all p s $\geq .09$, all η^2 s $\leq .002$). Missing data were accounted for using the full information maximum likelihood feature of Mplus, which uses all available information from the observed data to provide statistically appropriate standard errors (Brown et al., 2008).

Results

Descriptive Statistics

Table 1 includes the means, standard deviations, and correlations between our variables of interest. Of 860 total participants, there were 41 youths who experienced no early adverse events and 178 youths without prenatal substance exposure. Both the prenatal substance exposure and early adversity

Table 1
Descriptive Statistics and Correlations Among Study Variables

Variable	M	SD	Range	1	2	3	4	5	6	7	8	9	10	11
1. Early adversity	2.39	1.45	0 to 8	—										
2. Prenatal substance exposure	1.89	1.38	0 to 5	0.38***	—									
3. Prestress cortisol (raw value)	0.15	0.09	0.04 to 0.61	0.05	0.04	—								
4. First poststress cortisol sample (raw value)	0.16	0.10	0.04 to 0.66	-0.01	0.004	0.75***	—							
5. Second poststress cortisol sample (raw value)	0.15	0.10	0.03 to 0.61	-0.06	-0.03	0.58***	0.83***	—						
6. Cortisol intercept (prestress at 11 years; log-transformed)	-1.99	0.40	-3.10 to 0.62	0.04	0.03	0.92***	0.78***	0.64***	—					
7. Cortisol linear slope (cortisol reactivity at 11 years; log-transformed)	0.001	0.44	-2.07 to 1.94	-0.12***	-0.09**	-0.26***	0.28***	0.54***	-0.13***	—				
8. Externalizing behavior (11 years)	54.54	11.45	33 to 87	0.24***	0.18***	0.08*	-0.01	-0.06	0.07*	-0.16***	—			
9. Symptoms of externalizing psychopathology (11 years)	3.22	2.24	0 to 12.5	0.19***	0.19***	0.05	-0.01	-0.04	0.02	-0.10**	0.61***	—		
10. Executive function (11 years)	0.40	0.12	0.06 to 0.93	-0.14***	-0.06	-0.07*	0.002	-0.06	-0.06	0.12***	-0.14***	-0.12***	—	
11. Delinquency (11 years; square root transformed)	0.35	0.29	0 to 1.31	0.14***	0.10***	0.13***	0.06	0.01	0.13***	-0.12***	0.21***	0.36***	-0.11***	—
12. Quality of student-teacher relationship (11 years)	31.33	7.78	10 to 40	-0.11***	-0.05	-0.09*	-0.01	0.06	-0.06	0.13**	-0.31***	-0.20***	-0.17***	-0.10**

Note. Cortisol variables were log-transformed before running latent growth curve model.
p* < .05. *p* < .01. ****p* < .001.

variables are continuous. Inspection of data for outliers revealed that both variables are normally distributed. That the prenatal substance exposure variable was normally distributed is not surprising given that we oversampled for substance exposure in this study. A one-way analysis of variance revealed site differences in our prestress cortisol values, $F(3, 856) = 5.72, p < .001$. We therefore include site as a covariate in our growth models at the intercept. The majority of associations between our predictors (prenatal substance exposure and early adversity) and outcomes were significant. Greater prestress cortisol was associated with more externalizing behavior and more delinquency. Less cortisol reactivity was related to greater externalizing behavior on the CBCL, greater externalizing symptoms, and more delinquency, although greater cortisol reactivity was related to better executive function and a positive student-teacher relationship.

We used latent growth curve (LGC) modeling to examine children's cortisol response to the social stress task because of the dependency in the data (e.g., physiology nested within child over time). A major advantage of LGC modeling is the simultaneous estimation of both within-person effects and between-person effects. At Level 1, within-person variation in cortisol over time is modeled with individual-specific growth parameters (i.e., intercept and linear slope) that may vary across people. Level 2 covariates (e.g., prenatal substance exposure, early adversity) were used to predict interindividual differences in cortisol intercept and linear slope. We centered time so that the intercept reflected the prestress cortisol level. Weights of the two reactivity assessments were specified as the number of minutes that elapsed since the prestress cortisol assessment (.45 for the first reactivity assessment and .67 for the second reactivity assessment). We first examined unconditional growth models (i.e., with no predictors or covariates included in the model) for cortisol reactivity.

Models were tested examining the level and shape of children's cortisol trajectories during the social stress task. Our model included both random intercepts and slopes. Residual variances were held equal. The model that included a linear slope provided an excellent fit to the data, $\chi^2(3) = 8.00, p = .05$; comparative fit index (CFI; Bentler, 1990) = 0.99, and standardized root mean square residual (SMSR) = 0.03. There was no significant change in cortisol across the stress task. Children's prestress cortisol level was $-1.99 \mu\text{g/dl}$ (log-transformed), and the average rate of change in cortisol was $.001 \mu\text{g/dl}$ across the stress task. Significant variability, however, was found for

children's intercepts ($\sigma^2 = .18, p < .001$) and linear slopes ($\sigma^2 = .28, p < .001$).

Covariates

Because of the diurnal rhythm of cortisol, we included time of measurement as a time-varying covariate. We examined whether the time of each of the three assessments was associated with each measure of cortisol (e.g., whether time of the prestress measurement was correlated with the prestress cortisol value). Time of measurement was not significantly related with the time-specific measurement of cortisol (all $ps > .10$). We also examined whether prescription and/or nonprescription steroid medication impacted cortisol concentrations. Steroid use within the last 12 hr was not significantly associated with either the cortisol intercept ($b = .57, p = .16$) or slope ($b = -.06, p = .89$). No one reported eating or drinking beverages within an hour of the prestress sample or vigorous exercise within 1.75 hr of the prestress sample. Site was also included as a covariate given that there were differences in prestress cortisol across sites ($b = -1.4, p < .001$). There were no differences in cortisol reactivity across sites ($b = .01, p = .79$).

We also examined variables that have been shown in previous studies to covary with prestress cortisol and cortisol reactivity. These variables include child sex and race. In all models tested, race was a significant predictor of cortisol reactivity (linear slope), with African Americans exhibiting significantly less reactivity compared to Caucasians, Hispanics, and those who identified themselves as "other." We then ran multiple group structural equation models (SEMs) to explore these racial differences whereby African Americans were compared with non-African Americans (Caucasians, Hispanics, and those endorsing "other," as these groups did not differ with respect to cortisol reactivity). Race was not related to prenatal substance exposure ($b = -.01, p = .84$) or early adversity ($b = .02, p = .56$). However, when examining the variables that comprised the early adversity index, we found that African Americans (as compared to non-African Americans) were more likely to be poor and have a poorer quality home environment, though less likely to have CPS involvement.

Mediation Models

In all models described, we tested whether early adversity and cortisol reactivity mediated the effect of prenatal substance exposure on the following five outcomes (tested separately): (a) externalizing

behavior, (b) symptoms of externalizing psychopathology, (c) delinquency, (d) executive function, and (e) a positive student–teacher relationship, in a multiple group SEM framework. This approach allows us to examine whether the same structural model operates in different populations, in this case for African Americans and non-African Americans. Continuous variables were grand mean centered.

The models fit the data well: $\chi^2(29) = 53.91$, $p < .01$, CFI = .99, SMSR = .04 for externalizing behavior; $\chi^2(29) = 52.45$, $p < .01$, CFI = .98, SMSR = .04 for symptoms of externalizing psychopathology; $\chi^2(29) = 83.68$, $p < .01$, CFI = .97, SMSR = .05 for delinquency; $\chi^2(29) = 62.38$, $p < .001$, CFI = 0.98, SMSR = 0.04 for executive functioning; and $\chi^2(29) = 67.91$, $p < .001$, CFI = .98; SMSR = .04 for a positive student–teacher relationship. Results from all paths tested can be found in supplementary material found online. Significant effects related to study hypotheses are described next.

In all models tested among African Americans, site was a significant predictor of prestress cortisol. African American participants in Detroit had significantly higher prestress cortisol values than African American participants in Miami or Providence. African American participants in Memphis had significantly higher prestress cortisol values than participants in Providence. There were no differences in prestress cortisol between African American participants in Detroit or Memphis. Also among African Americans in all models tested, sex predicted cortisol reactivity, with females exhibiting more reactivity than males. Lower levels of prestress cortisol were related to more delinquency. Furthermore, greater prenatal substance exposure predicted greater exposure to early adversity. Finally in all models tested with African Americans, greater exposure to early adversity predicted less cortisol reactivity. Less cortisol reactivity was in turn related to greater externalizing behavior (Figure 1), more

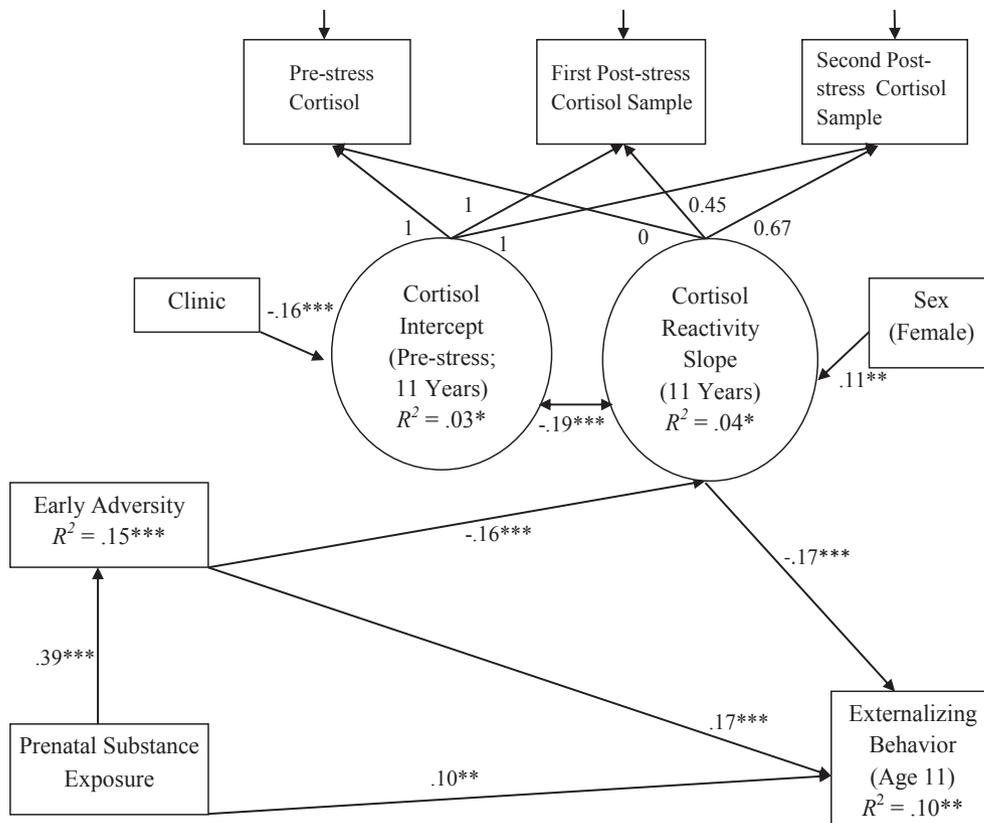


Figure 1. Effects of prenatal substance exposure, early adversity, and cortisol reactivity on externalizing behavior at age 11. Paths are standardized beta coefficients; $\chi^2(29) = 53.91$, $p < .01$; comparative fit index = 0.99; standardized root mean square residual = 0.04. All associations between covariates and growth factors were modeled. We only include the significant pathways for ease of presentation. Indirect effects of prenatal substance exposure on externalizing behavior through early adversity and cortisol reactivity were significant (standardized specific indirect path effects = .01, $p < .05$).

* $p < .05$. ** $p < .01$. *** $p < .001$.

symptoms of externalizing psychopathology (Figure 2), more delinquency (Figure 3), poorer executive functioning (Figure 4), and a less positive student-teacher relationship at age 11 (Figure 5).

Among non-African Americans, there were no significant predictors of prestress cortisol in any of the models tested. Only prenatal substance exposure predicted cortisol reactivity, with greater prenatal substance exposure predicting less cortisol reactivity. Higher levels of early adversity were related to greater externalizing behavior and externalizing symptoms, and a less positive student-teacher relationship at age 11. Greater prenatal substance exposure predicted more externalizing symptoms at age 11. There were no significant predictors of executive functioning or delinquency.

We also compared the chi-square values from these models with models in which relevant parameters were held equal across groups to test whether the multiple-group SEM models were significantly different between African Americans and non-African Americans. The differences in chi-square values were not significant in any of our models. Therefore, although there might be significant differences in the pathways from prenatal substance exposure to our outcomes between African Americans and non-African Americans, the difference between the parameters (e.g., prenatal substance exposure, early adversity, and cortisol slope) are not significant.

We then tested the indirect effect of prenatal substance exposure on our outcomes, separately

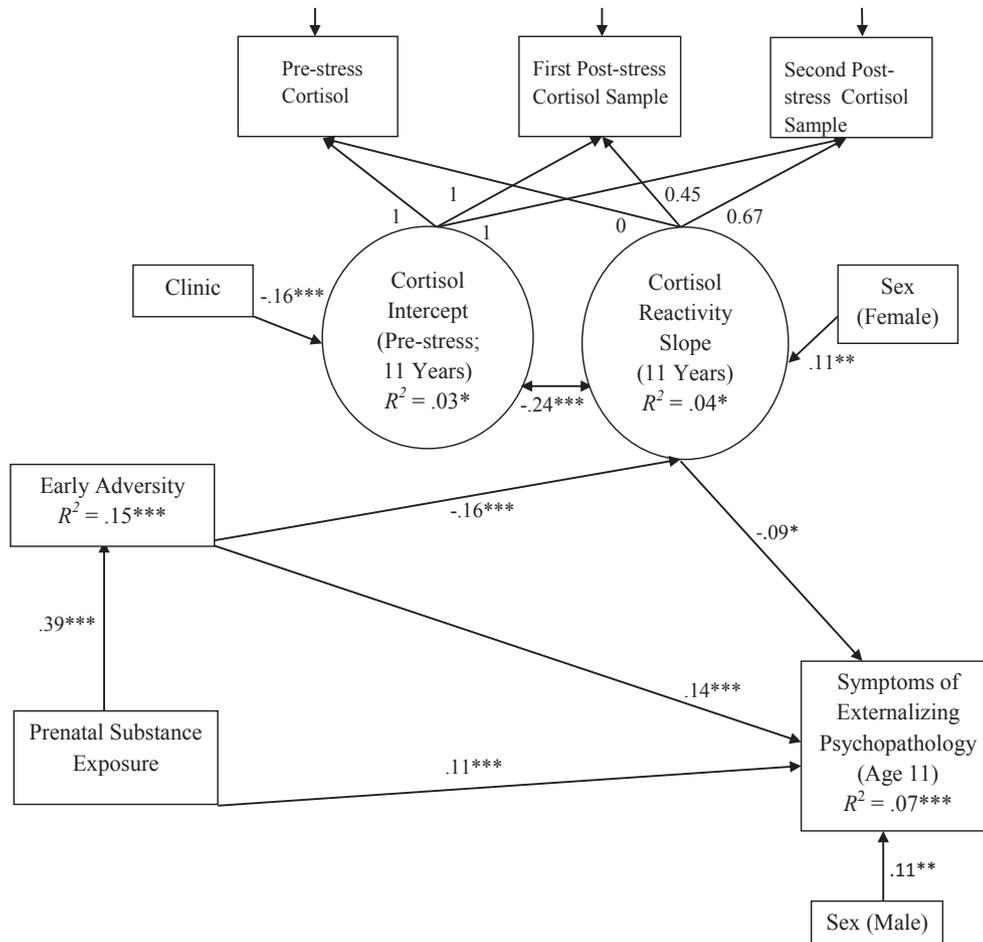


Figure 2. Effects of prenatal substance exposure, early adversity, and cortisol reactivity on symptoms of externalizing psychopathology at age 11. Paths are standardized beta coefficients; $\chi^2(29) = 52.45, p < .01$; comparative fit index = 0.98; standardized root mean square residual = 0.04. All associations between covariates and growth factors were modeled. We only include the significant pathways for ease of presentation. Indirect effects of prenatal substance exposure on symptoms of externalizing psychopathology through early adversity and cortisol reactivity were not significant.

* $p < .05$. ** $p < .01$. *** $p < .001$.

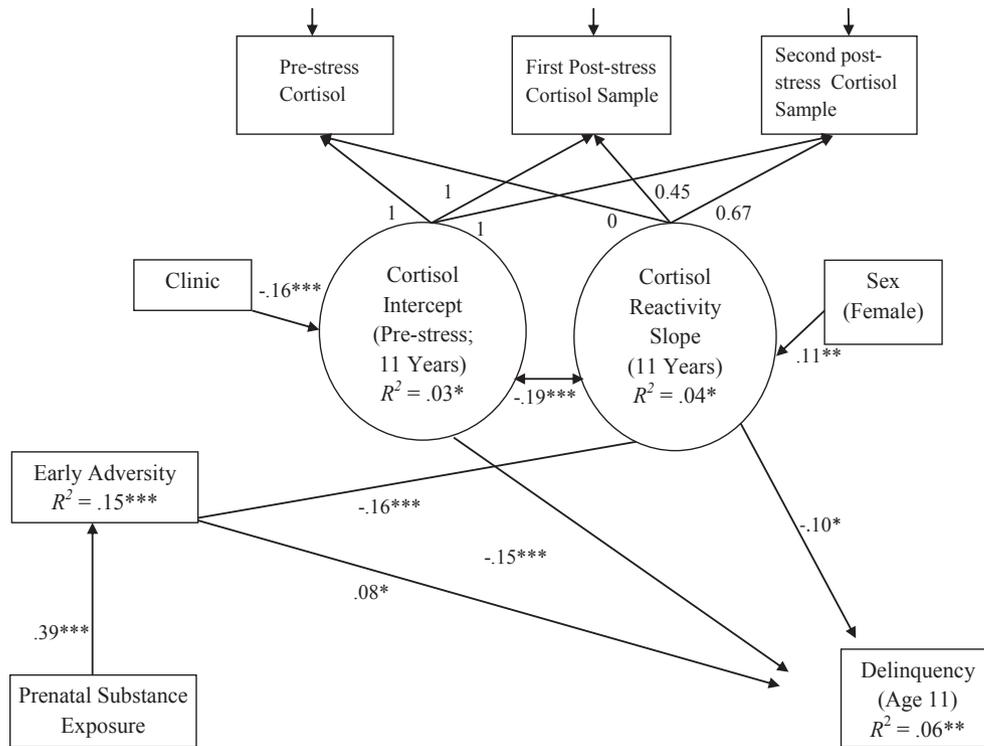


Figure 3. Effects of prenatal substance exposure, early adversity, and cortisol reactivity on delinquency at age 11. Paths are standardized beta coefficients; $\chi^2(29) = 83.68, p < .001$; comparative fit index = 0.97; standardized root mean square residual = 0.05. All associations between covariates and growth factors were modeled. We only include the significant pathways for ease of presentation. Indirect effects of prenatal substance exposure delinquency through early adversity and cortisol reactivity were marginal (standardized specific indirect path effects = .01, $p = .08$). * $p < .05$. ** $p < .01$. *** $p < .001$.

for African Americans and non-African Americans, through both early adversity and cortisol, controlling for site (at the prestress assessment) and sex. We tested indirect effects using the Sobel test in Mplus following MacKinnon's (2008) conceptualization of mediation. Prenatal substance exposure had a significant indirect influence through early adversity and cortisol reactivity on externalizing behavior, executive functioning, and a positive student-teacher relationship at age 11, accounting for 5.94%, 25%, and 19.53% of the total effect of prenatal substance exposure on externalizing behavior, executive functioning, and a positive student-teacher relationship, respectively (see Table 2). Prenatal substance exposure had a marginally significant indirect influence, through early adversity and cortisol reactivity, on delinquency at age 11, accounting for 4.54% of the total effect of prenatal substance exposure on delinquency. Tests of mediation were not significant for symptoms of externalizing psychopathology. There were no significant mediators among non-African Americans.

Discussion

Although it is understood that adversity both in the form of prenatal substance exposure and postnatal early stressful experiences contributes to the development of problem behavior, the developmental processes involved are much less clear. The theory of allostatic load suggests that the effects of early life stress should manifest later in life in the form of physiological dysregulation, which in the case of the neuroendocrine system frequently involves a dampening or blunting of the neuroendocrine response to stress. The attenuation hypothesis builds on this theory to suggest specific pathways involving both prenatal biological risk and early adversity as they impact the stress response system and ultimately problem behavior. However, there is a critical gap in our understanding of how this process unfolds, particularly in early adolescence, a time of significant brain development (Dahl, 2004). Furthermore, we know of no studies that have been able to empirically test the attenuation hypothesis incorporating adversity effects in the form of prena-

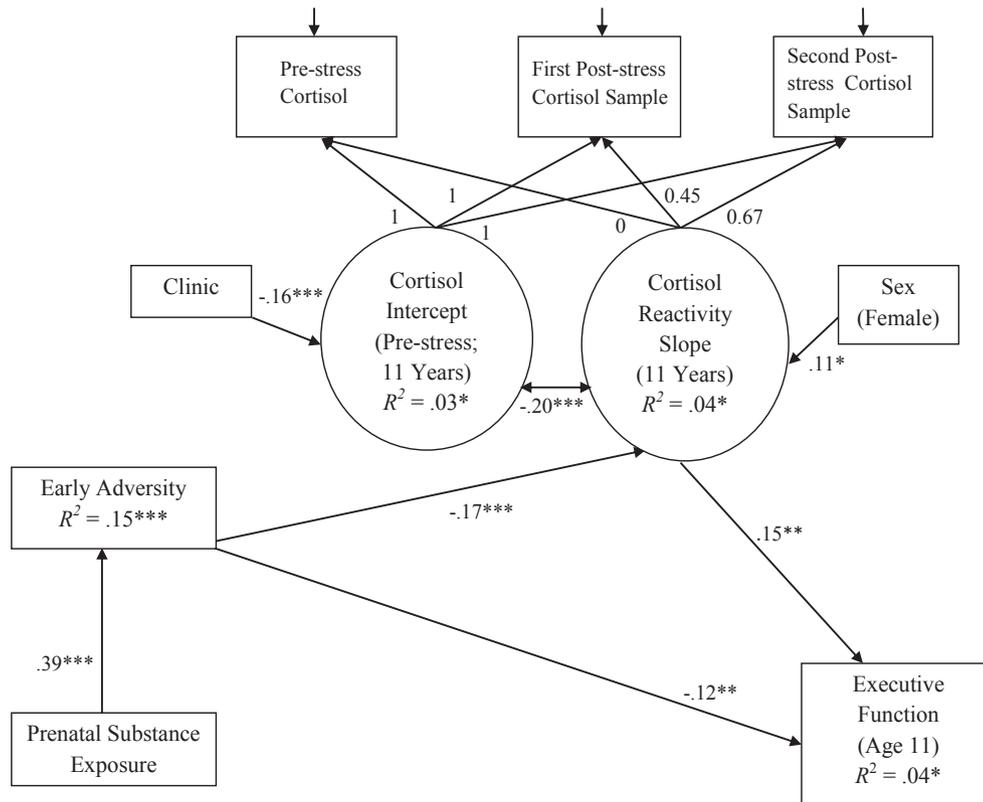


Figure 4. Effects of prenatal substance exposure, early adversity, and cortisol reactivity on executive function at age 11. Paths are standardized beta coefficients; $\chi^2(29) = 62.38, p < .01$; comparative fit index = 0.98; standardized root mean square residual = 0.04. All associations between covariates and growth factors were modeled. We only include the significant pathways for ease of presentation. Indirect effects of prenatal substance exposure on executive function through early adversity and cortisol reactivity were significant (standardized specific indirect path effects = .01, $p < .05$).

* $p < .05$. ** $p < .01$. *** $p < .001$.

tal substance exposure and early postnatal adversity as predictors of later adolescent behavior. This study addressed these gaps by investigating cortisol reactivity as a mediator of the relation between early adversity (including both prenatal substance exposure and early life stress) and various indices of problem behavior in adolescence. We found indirect effects of early adversity on externalizing behavior, executive functioning, and a positive student–teacher relationship, via LHPA axis functioning, but only for African Americans. These results shed light on how adverse experiences early in life may impact the development of problem behavior and adaptive behavior in adolescence through disruptions in the neuroendocrine system.

Our findings rather consistently supported the attenuation hypothesis proffered by Susman (2006). Across a range of outcomes spanning both the components of neurobehavioral disinhibition and a positive student–teacher relationship, we found that higher levels of prenatal substance exposure were

related to greater levels of postnatal early adversity (birth to age 6). This association is not surprising, given that children with prenatal substance exposure are more likely to grow up in poverty, be raised by a caregiver with some form of psychopathology, and face caregiver instability compared to children without prenatal substance exposure (Hans, 1999). Among African Americans, greater exposure to early adversity in turn was consistently associated with decreased cortisol reactivity (i.e., attenuation), though no effect was found on pre-stress cortisol levels. These results are in accordance with previous studies demonstrating that high levels of stress experienced repeatedly early in life leads to dampening of the LHPA axis in response to stress (Fisher et al., 2006; Lester et al., 2010). Attenuation of cortisol reactivity in turn was related to higher levels of externalizing behavior, poorer executive functioning, and a less positive student–teacher relationship. Notably, among African Americans, there was a significant indirect effect of both

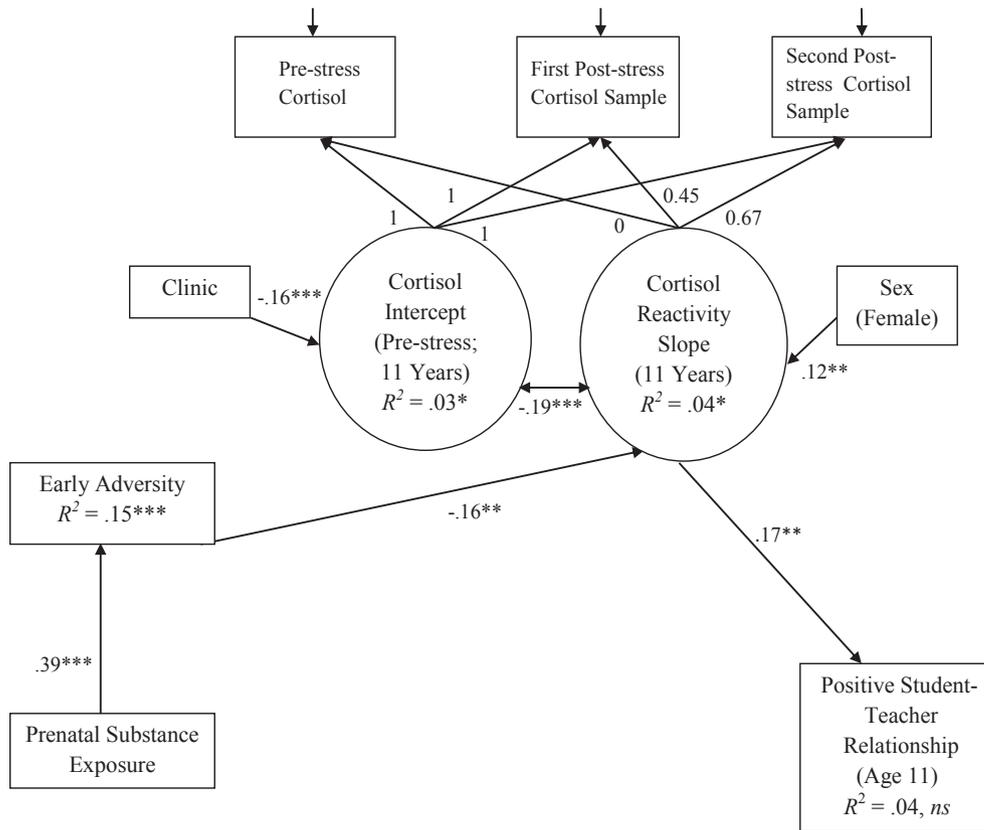


Figure 5. Effects of prenatal substance exposure, early adversity, and cortisol reactivity on a positive student–teacher relationship at age 11. Paths are standardized beta coefficients; $\chi^2(29) = 67.91, p < .001$; comparative fit index = 0.98; standardized root mean square residual = 0.04. All associations between covariates and growth factors were modeled. We only include the significant pathways for ease of presentation. Indirect effects of prenatal substance exposure on a positive student–teacher relationship through early adversity and cortisol reactivity were significant (standardized specific indirect path effects = $-.01, p < .05$). * $p < .05$. ** $p < .01$. *** $p < .001$.

prenatal substance exposure and early adversity on three of the five outcomes tested via the LHPA axis response to stress, and a marginal effect on delinquency.

It is possible that exposure to substances prenatally altered the cortisol response to stress. We have argued elsewhere (Lester, Marsit, Conradt, Bromer, & Padbury, 2012; Lester & Padbury, 2009) that in addition to the specific mechanisms of action, adverse intrauterine exposure to drugs can act as a prenatal stressor and lead to increases in the release of fetal catecholamines (epinephrine, norepinephrine, and dopamine) and glucocorticoids. These catecholamines in turn alter regulation of the neuroendocrine environment by acting on the LHPA axis resulting in modified set points for physiologic, metabolic, and behavioral outcomes. Thus, this conceptualization of prenatal substance exposure as a prenatal stressor fits with the allostatic

load framework by suggesting that allostatic processes, and the alteration of physiologic set points, may be initiated prenatally (Lester & Padbury, 2009). Therefore, by birth, infants with prenatal substance exposure may be more biologically vulnerable to postnatal stress given their increased exposure to cortisol prenatally. Indeed, evidence supporting this hypothesis comes from Eiden et al. (2009) who found that infants with prenatal substance exposure exhibited greater cortisol reactivity at 7 months of age. In addition, as most women who use drugs prenatally use more than one substance, we conceptualize prenatal substance exposure as a cumulative stress model whereby exposure to substances prenatally is additive. This model has been used to examine changes in the parasympathetic response to stress (Conradt et al., 2013), as well as changes in neurobehavioral disinhibition (Fisher et al., 2011). Our results support

Table 2
Standardized Specific Indirect Path Effects of Early Adversity on Outcomes at Age 11

	Estimate	SE	Estimate/SE
Among African Americans			
PSE → early adversity → prestress cortisol → externalizing behavior	0.002	0.001	1.08
PSE → early adversity → cortisol reactivity → externalizing behavior	0.01	0.01	2.32*
PSE → early adversity → prestress cortisol → delinquency	0.004	0.003	1.47
PSE → early adversity → cortisol reactivity → delinquency	0.01	0.004	1.76 [†]
PSE → early adversity → prestress cortisol → executive function	0.001	0.002	0.44
PSE → early adversity → cortisol reactivity → executive function	0.01	0.01	2.00*
PSE → early adversity → prestress cortisol → positive student–teacher relationship	–0.001	0.002	–0.89
PSE → early adversity → cortisol reactivity → positive student–teacher relationship	–0.01	0.01	–2.03*
Among non–African Americans			
PSE → early adversity → prestress cortisol → externalizing behavior	–0.001	0.002	–0.37
PSE → early adversity → cortisol reactivity → externalizing behavior	0.001	0.003	0.25
PSE → early adversity → prestress cortisol → delinquency	0.000	0.001	–0.18
PSE → early adversity → cortisol reactivity → delinquency	0.001	0.003	0.28
PSE → early adversity → prestress cortisol → executive function	–0.001	0.003	–0.41
PSE → early adversity → cortisol reactivity → executive function	0.000	0.001	0.06
PSE → early adversity → prestress cortisol → positive student–teacher relationship	0.001	0.003	0.39
PSE → early adversity → cortisol reactivity → positive student–teacher relationship	0.000	0.002	–0.22

Note. PSE = prenatal substance exposure.

[†] $p \leq .08$. * $p < .05$.

this conceptualization by demonstrating that a cumulative stress model of prenatal substance exposure exerted indirect effects on most of our outcomes through exposure to early adversity and the cortisol response to stress.

Although at first prenatal substance exposure may be associated with greater cortisol reactivity, over time and with exposure to early adversity that so often accompanies prenatal substance exposure, the cortisol response may become blunted, or attenuated. Unfortunately it is unclear from this study at what point in time attenuation of the cortisol response may have occurred, if at all. Perhaps heightened cortisol reactivity in infancy (Eiden et al., 2009) leads to blunted cortisol responses in adolescence (Lester et al., 2010) among children with prenatal substance exposure who are also exposed to early adversity in form of primary caregiver changes (Eiden et al., 2009) or domestic violence (Lester et al., 2010). Support for this hypothesis comes from the present study as well as from others that do not include prenatal substance exposure, though effects of early adversity are modeled. For example, Davies et al. (2007) found an indirect effect of marital conflict in kindergarten on externalizing behavior 2 years later via a dampened, or attenuated, cortisol response to stress.

If cortisol attenuation did result from repeated exposure to adverse experiences early in life, as the-

ory and empirical support suggest, how does this process unfold? Susman (2006) argues that early experiences with caregivers and with the broader caregiving environment that are unpredictable and threatening may disrupt limbic system activity, which mediates the LHPA axis response to stress. This process may actually be adaptive, as it leads to suppression of the arousal response to stress in order to prevent chronic behavioral and endocrine overactivity. However, in this study, this attenuated response to stress did not appear to be adaptive, as it was associated with greater externalizing behavior, poorer executive functioning, delinquency, and a less positive student–teacher relationship.

The degree to which early adversity and cortisol reactivity mediated the relation between prenatal substance exposure and our outcomes was quite variable, with the largest proportion of mediated effects found for our adaptive outcomes: executive functioning and a positive student–teacher relationship. In the short term, increases in cortisol in response to stress are related to synaptic long-term potentiation, memory, and attention, all of which may directly support executive functioning and which can support attention and behavior regulation among students in the classroom. With time, however, the strength of the relation between cortisol reactivity and externalizing behavior should increase, as with repeated activation of the

neuroendocrine system, a hypocortisolism response could become stronger. Thus, we may be identifying the initial hypocortisolism–externalizing behavior link at age 11, but with time, the strength of the association may increase.

Importantly, this dampening of the cortisol response to stress was found only among African American youths, and not among Caucasians, Hispanics, and individuals self-identified as coming from another racial group. This finding is consistent with previous work indicating that a flattened, or blunted, diurnal pattern, or lower levels of the cortisol awakening response are found among African Americans, but not individuals from other racial groups (DeSantis et al., 2007; Hajat et al., 2010; McCallum et al., 2006). That we have found a similar blunted, or hypocortisolism, response at age 11 suggests that early adverse experiences, accumulated during the first 6 years of life, have already become biologically embedded to disrupt the LHPA axis. As there were no differences in the number of early adverse exposures or prenatal substance exposure among African Americans and non-African Americans, there may be an unaccounted-for construct that is affecting the LHPA response among African Americans, such as the experience of racism, which has documented effects on the LHPA axis (Clark, Anderson, Clark, & Williams, 1999). On the other hand, as some components of our early adversity measure were related to race (e.g., poverty and a poor quality home environment), it may be that exposure to these adversities contributed to the hypocortisolism response seen among African Americans.

An unexpected finding involved the differential effects of prenatal substance exposure and early adversity on cortisol reactivity. Among African Americans, only early adversity, but not prenatal substance exposure, predicted hypocortisolism, although the opposite was the case for non-African Americans. Prenatal substance exposure in isolation may be related to cortisol reactivity in all racial groups studied. However, the effects of early adversity may trump those of prenatal substance exposure, but only among African Americans who may have experienced these stressors differently. In other words, although all racial groups may have experienced the same number of stressors, perhaps the severity of the experience was exacerbated among African Americans by an unobserved variable.

We have also added to the literature by identifying processes involved in the development of positive adaptation in this population of adolescents at risk due to prenatal substance exposure. It is impor-

tant to identify correlates of positive outcomes in this population to better understand the pathways that lead to positive outcomes children at risk due to exposure to substances prenatally. In this study, among African Americans, greater levels of cortisol reactivity were related to a more positive student–teacher relationship at age 11. In addition to adding to our knowledge of processes of positive adaptation in this population, this result is also important from a biobehavioral perspective. There is very little work in the physiological literature examining neuroendocrine predictors of positive adaptation; most studies examine the absence of a negative outcome as an indicator of resilience or adaptation (though, for an exception, see Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010). Results from this study suggest that the ability to mount a cortisol response to stress may reflect more effective self-regulatory skills (Blair et al., 2005). Moderate increases in cortisol reactivity are seen as adaptive, increasing alertness, enhancing memory, and aiding in problem solving during stressful situations (Susman, 2006). These qualities are important in developing positive, supportive relationships with adults such as teachers. In addition, the ability to negotiate a positive relationship with a teacher may also reflect a generalized ability for adequately navigating social relationships (Adam, 2006). Thus, our findings suggest that adolescents whose LHPA axis is responsive to a salient social stressor may have the ability to flexibly respond to psychosocial stress, enhancing self-regulatory skills and the ability to build and maintain positive relationships with teachers.

Although we interpret the associations between greater cortisol reactivity and a positive student–teacher relationship as adaptive, it may very well instead be an atypical response suggestive of hypercortisolism. A major impediment to the psychophysiology field is a lack of information regarding what a “normative” response to stress is. Although studies suggest that mobilizing a neuroendocrine response (as opposed to not responding or exhibiting a decrease in cortisol) to a salient stressor such as the Trier Social Stress Task is healthy, it is unclear from these results where the line is drawn between a “healthy” response and a “hypercortisolism” response to stress (Davies et al., 2007).

These findings should be interpreted within the context of study limitations. First, we cannot determine the direction of effect with these data, as our mediator and outcome variables were measured at the same point in time. Although theory and empirical evidence suggest that individual differences in cortisol reactivity are predictive of pertinent psycho-

social outcomes, it is also possible that individual differences in behavior entrain the LHPA response so that, over time, attenuation of the cortisol response occurs. Future work should assess children's cortisol reactivity over multiple points in development to determine whether LHPA functioning earlier in life predicts behavioral outcomes over and above current LHPA activity. Relatedly, given our interest in early adversity, we did not model whether adverse experiences that occurred later in life, between ages 6 and 11, could have affected our outcomes at age 11. Future work will test whether concurrent levels of life stress exert as strong of an effect on behavioral outcomes as early experiences of adversity. Second, only one measure of physiology was used in the current study. Independent physiological indices of allostatic load, such as the parasympathetic system, should be used in future studies to corroborate our LHPA findings. Third, we did not isolate the effects of a single substance, such as cocaine, on cortisol reactivity, and instead used a more ecologically valid indicator of prenatal substance use. We acknowledge that a limitation for this approach is that the mechanism of action of these drugs is different, and we cannot determine/estimate the relative impact of one substance over another. Fourth, our measure of early adversity does not allow us to conclude what specific adversity variable may be more of a contributor to cortisol reactivity than others. A cumulative risk index does, however, allow for the simultaneous examination of multiple correlated risk factors, with poorer outcomes expected for children exposed to greater risk.

This multimethod study is the first to identify environmental and physiological processes related to both adaptation and maladaptation among adolescents with prenatal substance exposure. This work is also promising as it suggests a pathway to positive outcomes among children with prenatal substance exposure through neuroendocrine functioning. These findings are particularly salient as they suggest that environmental adversity in the form of prenatal substance exposure and early life stress become biologically embedded to affect individual differences in the LHPA axis, already by age 11. These results add to the body of work indicating that a decreased or blunted cortisol response to stress may be a biological marker that can aid in the identification of children at risk for problem behavior (Shonkoff, Boyce, & McEwen, 2009). That an attenuated or blunted cortisol response was indicative of greater externalizing behavior, poorer executive function, and delinquency already at age 11 suggests that intervening to prevent the develop-

ment of problem behavior before age 11 is warranted.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Parameter Estimates and Standard Errors for Predicting Study Outcomes