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Prenatal Cocaine Exposure, Gender, and Adolescent Stress Response: A Prospective Longitudinal Study

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Abstract

Prenatal cocaine exposure is associated with alterations in arousal regulation in response to stress in young children. However, relations between cocaine exposure and stress response in adolescence have not been examined. We examined salivary cortisol, self-reported emotion, heart rate, and blood pressure (BP) responses to the Trier Social Stress Test (TSST) in 49 Prenatally Cocaine and other drug Exposed (PCE) and 33 Non Cocaine Exposed (NCE) adolescents. PCE adolescents had higher cortisol levels before and after stress exposure than NCE adolescents. PCE girls showed an elevated anxiety response to stress (compared to NCE girls) and PCE boys showed a dampened diastolic BP response (compared to NCE boys). Girls showed higher anger response and lower pre-stress systolic BP than boys. Group differences were found controlling for potential confounding variables and were not moderated by caregiver-child relationship quality (although relationship quality predicted HPA-Axis and anxiety response). Findings suggest that prenatal drug exposure is associated with altered stress response in adolescence and that gender moderates this association.

Keywords

Prenatal cocaine exposure; Stress response; Cortisol; Emotion; Sex differences

1. Introduction

The epidemic of crack-cocaine use in the late 1980's and early 1990's has led researchers to examine the relationship between prenatal cocaine exposure and children's development. Findings regarding prenatal cocaine effects on cognitive, motor, and language development have been inconsistent, with many studies findings no or small effects [27,75,78; but for

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exception, see 5]. However, prenatal cocaine exposure may be associated with alterations in children's attentional and emotional regulation [14,27,56,73]. This may occur either through direct teratogenic effects, through genetic transmission of arousal regulatory problems, or through chronic environmental stressors experienced postnatally by cocaine-exposed children, including dysfunctional parenting and chaotic home environments. Additionally, cocaine using mothers most often use other drugs in pregnancy as well, meaning that prenatally "cocaine exposed" children are typically exposed to multiple drugs which may have separate or interactive teratogenic effects. The present study examined emotional, neuro-endocrine (Hypothalamic Pituitary Adrenal [HPA] axis), and autonomic (heart rate, blood pressure) responses to a stressor in low income adolescents who were prenatally cocaine and other drug exposed (PCE) or were non cocaine exposed (NCE) and who were followed since birth.

A number of human and animal studies have examined relations between prenatal cocaine exposure and reactivity to stress. However, thus far, human studies are largely limited to early childhood. The existing research suggests that prenatal cocaine exposure may alter developing emotional arousal and regulation systems, including monoaminergic neurotransmitters systems in the mesocortical and mesolimbic areas [28,56,62,68,74]. Behaviorally, prenatally cocaine exposed animals show an altered pattern of response following stressful conditions such as forced swim or footshock, which may indicate over-arousal and a lack of adaptation to stress [17,29,61,77].

Cocaine exposed human infants and preschoolers are found to be more excitable and show greater irritability/frustration than non-exposed children in response to stressors such as the still face or toy wait task paradigms [10,20,22(particularly for boys), 57,58], although some research finds reduced emotional expressions in cocaine-exposed infants [2]. Cocaine exposed youth's self-reported emotions in response to stress have not typically been studied in part because of a focus on younger children thus far in the published literature. However, we might expect cocaine exposed children to also show greater self-reported negative emotion under stress or challenge than non-cocaine exposed children.

In addition to emotional responses to stress, HPA axis response to stress may be altered by prenatal cocaine exposure [56,71]. Prenatal cocaine exposure has been related to increased basal corticosterone levels in animals [49]. In humans, there are five published studies of HPA axis response and cocaine exposure, four of which are with infants. One study of healthy preterm infants found no differences in basal cortisol levels, but lower cortisol levels following stressors (neurobehavioral examination, heel prick) in cocaine-exposed than non-exposed infants [54]. Another study found lower baseline cortisol levels for cocaine-exposed infants, but no differences in cortisol levels following a stressor (a blood draw) [38]. A third study found higher resting cortisol levels in cocaine-exposed versus non-exposed preterm infants [65]. The fourth study found no differences in pre-stress cortisol but higher cortisol reactivity following emotional tasks (arm restraint, puppet show, viewing scary masks) for cocaine-exposed than non-exposed infants (particularly cocaine exposed boys) [25]. A recent study of 11-year olds found that cocaine-exposed youth were more likely to show a decreased or blunted cortisol response from pre- to post-stressor, particularly if they also had been exposed to domestic violence [50]. Thus, results have been mixed, with some studies showing lower cortisol at rest or in response to stress and others showing higher cortisol at rest or in response to stress. However, all studies suggest some alteration of the HPA axis system, at least in infancy and into late childhood.

In addition to HPA axis response, research suggests that cocaine exposure may be related to altered autonomic response to stress. PCE human infants show higher heart rate response [6, 67] and less suppression of parasympathetic markers [67] in stressful conditions than non-exposed infants. Little research has been conducted beyond infancy. One study found greater

increases in skin conductance levels from baseline to stressor in cocaine exposed 8 year olds as compared to controls [39].

In sum, cocaine exposure may be associated with alterations in emotional arousal, HPA axis, and cardiovascular response to stressors in early childhood. However, it is not known whether these alterations in stress response persist into adolescence. It is important to examine stress response in adolescence for several reasons. First, adolescence is a critical period for the maturation of brain regions involved in emotional and stress regulation. During adolescence, sub-cortical regions involved in emotional arousal are activated (due in part to increases in sex steroid hormones) at the same time as the prefrontal cortex is still developing [18,70]. Second, in adolescence, there are several life stressors/transitions which challenge adolescents' developing regulatory systems, including pubertal development, school transitions, and changing relationships with peers and parents [24]. Third, several stress-related psychological disorders emerge in adolescence, including depression and, in late adolescence, substance use disorders (33,55).

In examining stress response, it is also important to take into account gender. Girls typically report greater emotional experience than boys, particularly for anxiety, fear, and sadness [13]. However, this may differ depending on socio-economic group [60]. Girls also show a greater heart rate response to stress than boys [45] and may show greater resting cortisol levels [44]. Also, the relation between cocaine exposure and stress response may differ by gender. For example, in middle childhood, PCE boys, but not girls, show elevated externalizing behavior problems as compared to non-exposed children [21].

The present study examined HPA axis, self-reported emotional, and physiological arousal in response to a standardized social stressor (the Trier Social Stress Test [16]) in a sample of low-income adolescents who were followed prospectively since birth and who were prenatally cocaine (and other drug) exposed (PCE) or who were non cocaine exposed (NCE). The NCE group included youth who were exposed either to no substances or to small amounts of alcohol, tobacco, or marijuana in utero. We examined associations between stress response and PCE group, gender, and the interaction between PCE group and gender. We hypothesized that: 1. PCE adolescents would show greater HPA axis response to the stressor as compared to NCE adolescents; 2. PCE adolescents would show greater self-reported emotional and heart rate response, particularly for girls; 3. PCE adolescents may show greater blood pressure response as compared to NCE adolescents.

We also examined whether PCE group differences were moderated by caregiver-child relationship quality, as negative caregiving may exacerbate "effects" of cocaine and other drug exposure [4,9] and caregiving quality may affect stress response [53]. Also, given that cocaine-using mothers typically use other substances during pregnancy and that cocaine exposure is associated with birth-related risk factors (e.g., lower birth weight [8]), we considered mothers' other substance use and birth conditions for inclusion as control variables in analyses.

2. Method

2.1 Participants

Participants were drawn from a larger longitudinal study of the emotional and cognitive development of cocaine and other drug exposed and non cocaine exposed children. Children in the larger study cohort (N = 371) were followed since birth, with biannual assessments. Youth in the larger cohort ranged in age from 11-17 and those who were aged 14 ½ to 16 years were invited to join the present laboratory stress study if they met criteria for the laboratory study (no acute serious psychiatric condition, no serious medical condition, and IQ > 80). Based on these criteria, eight adolescents (9%) were excluded- four for acute psychiatric disorders

requiring multiple psychotropic medications (e.g., bipolar disorder, PTSD), one for HIV+ diagnosis, one for insulin-dependent diabetes, and two for IQ's < 80. Eighty two adolescents aged 14 ½ to 16 years met the criteria and were invited to participate. Of these 82, all agreed to participate in the study. These 82 were not different from the overall sample of 371 on demographic variables (sex, race, mother education level), obstetric complications, or mother cocaine use in pregnancy (p 's > .41).

The 82 participants in the present study had a mean age of 14.95 years ($SD = .82$ years), range from 14.5-16 years, with one 17-year-old). Forty nine were Prenatally Cocaine and other drug Exposed (PCE) and 33 were Non Cocaine Exposed (NCE) (PCE children were originally over-sampled in anticipation of greater attrition in that group). Adolescents in the NCE group included those without any exposure to substances and also those with a low level of exposure to alcohol, tobacco, or marijuana (less than 2 days per month). Caregivers accompanying the adolescents to the present study were their current primary caregivers. These were mostly biological mothers (80.5%), with 7.3% grandmothers, 3.7% biological fathers, 3.7% aunts, 2.4% familial foster care parents (aunts and grandmothers), and 2.4% non-familial foster care or adoptive mothers.

2.2 Drug Exposure Categorization

Participants' mothers were recruited over a five-year period from women registering for prenatal care at the Women's Center of a large urban hospital in the Northeast and, for those who did not receive prenatal care, upon admission to the postpartum ward. The Women's Center provided care primarily for inner-city women and served a low-income, primarily minority, population. Women were screened for substance use by trained research associates. Self-report information was obtained through a detailed interview (based on the Addiction Severity Index-ASI [59]) that covered lifetime use (number of years using) and frequency and amount of use in the previous 30 days for cocaine, tobacco, alcohol, marijuana, and other drugs (e.g., sedatives and opiates). Interviews were conducted either during the first prenatal visit or (for those not receiving prenatal care) immediately following delivery. For all women, regardless of reported drug use, urine samples were obtained for toxicology either several times throughout the pregnancy (for those women attending prenatal visits) and/or at delivery (for those not receiving prenatal care). Every mother and infant had a urine screen at delivery. Urine was screened for metabolites of cocaine (e.g., benzoylecognine), opioids, benzodiazepines, and marijuana, using the Abbott TDx system and the recommended cutoff levels [63].

Mothers were considered to be in the cocaine and other drug using group (PCE) if they reported cocaine use during pregnancy even if in those instances, urine or meconium toxicological results were negative. Also, if mothers reported that they did not use cocaine, but urine toxicological results were positive for cocaine, infants were considered exposed. Mothers who used opiates were excluded from the study. As cocaine use frequently co-occurs with use of tobacco, alcohol and/or marijuana [76], mothers in the cocaine using group were not excluded if they used these other substances, and other drug use was considered for inclusion as a covariate in analyses. Non-cocaine using women were eligible for recruitment into the comparison group, NCE, which included women who used small amounts of alcohol, tobacco, and/or marijuana during pregnancy (< two days per month) and women who did not use.

2.3 Demographic, Birth Status, and Caregiving Quality Information

Demographic, birth status, and parent-child relationship quality scores are shown in Table 1. Forty nine percent of the overall sample was male, with no exposure group differences in child gender. There were exposure group differences in mother education level, with fewer mothers completing high school in the PCE group than the NCE group (no mothers reported education beyond high school).

Scores on the Obstetric Complications Scale (OCS [52]) are also listed in Table 1. The OCS is a checklist of the number of favorable conditions (out of 41 conditions) during the pregnancy and delivery, including birth weight, gestation age, parity, mother age, bleeding during pregnancy, and infections or acute medical conditions during pregnancy. Higher scores on the OCS represent more optimal birth factors. The OCS was completed through mother interview and medical chart abstraction. OCS scores were calculated as the percentage of optimal scores and then changed to the “converted raw score”, following Littman and Parmelee [52].

Caregiver-child relationship quality was measured by the Parenting Stress Index (PSI)'s parent child relationship subscale (PCR). The Parenting Stress Index is a widely-used caregiver-report measure of parenting stress and parent-child relationship quality. The parent-child relationship (PCR) subscale measures caregivers' dissatisfaction with their interactions with their children and with their children generally. Higher scores on this measure indicate a more problematic caregiver-child relationship. The PCR subscale has shown good reliability and validity, correlating with self-reported and observed parenting behavior [34,69]. Primary caregivers completed the PSI at a session prior to the laboratory stress session. In this study, the child version of the parenting stress index [1] was used at first and then was switched to the adolescent version [69] partway through the study (52 adolescents had child version data and 27 had adolescent version data, 3 were missing PSI data). The PCR subscale in the child version had 12 items, whereas the adolescent version had 16 items. Because of the different numbers of items, an average score for the subscale was used in analyses.

2.4 Mothers' Substance Use during Pregnancy

Mothers' reported levels of cocaine and other drug use in the previous 30 days was obtained through interviews during pregnancy or at delivery. Substance use information for PCE and NCE mothers is provided in Table 2. PCE mothers reported using cocaine an average of 5.53 days per month ($SD = 5.54$ days) and used an average of .78 grams ($SD = 1.47$ grams) per occasion. PCE mothers reported using cocaine for an average of 4.93 years ($SD = 3.04$). PCE mothers in this study typically reported that they used cocaine in the early months and throughout their pregnancy. PCE mothers were more likely than NCE mothers to report use of alcohol, tobacco, and marijuana. The PCE mothers also used alcohol, tobacco, and marijuana more frequently than NCE mothers during pregnancy (see Table 2).

2.5 Procedure

Adolescents attended four sessions, spaced about one week apart. In the first two sessions, youth completed questionnaires, computer tasks, and interviews assessing cognitive and emotional functioning and psychiatric disorders. The adolescents' primary caregivers completed the Parenting Stress Index and a questionnaire on adolescent temperament. In the third, the laboratory stress session, adolescents completed the Trier Social Stress Test. The present study focuses on this session. Adolescents and caregivers were compensated \$50 and \$25 respectively for each session, with an additional bonus payment for completing all sessions. An additional \$25 was provided for caregivers to complete the caregiver questionnaires. Participating families were compensated for transportation costs. Informed parental consent and adolescent assent was obtained and the study protocol was approved by the University's Institutional Review Board.

2.5.1 Laboratory stress session—On the laboratory day, adolescents arrived at 4pm. Adolescents were brought into the testing room and seated at a table. A blood pressure cuff was placed on the adolescent's preferred arm to monitor blood pressure and a pulse sensor was placed on the adolescent's forefinger on the non-writing hand to obtain a measure of heart rate.

Adolescents were asked to have a snack one hour prior to the session and were not allowed to eat during the session. Youth were asked to refrain from alcohol or drug use prior to the session to control for acute drug effects on physiology and HPA axis functioning and urine specimens and breathalyzers were conducted on all adolescents to assess recent substance use.

Adolescents were asked about their medication use on the day of the laboratory session, since medication use may alter stress response [36]. Seven adolescents reported taking medications. One reported using Motrin, one used Tylenol Allergy, one used Albuterol, one used Clindamycin, and one used Albuterol, Singulair and Flonase. Medication use did not differ by exposure group ($\chi^2 [83] = .26, ns$) or by child sex ($\chi^2 [83] = .004, ns$). Medication use was related at a trend level ($p < .10$) to anxiety scores in the laboratory session, with those using medication reporting lower anxiety across the timepoints. Given the trend-level relations between medication use and stress response variables, we included medication use (Y/N) as a control variable in all analyses. In addition to this reported medication use, three girls reported hormonal birth control use. Use of hormonal birth control did not differ for girls in the PCE versus NCE group ($\chi^2 [43] = .75, ns$) and birth control was not related to outcome variables and so was not included as a control variable in analyses.

The laboratory session began at 4:15pm. From 4:15- 4:55pm, there was an adaptation period during which the participants were lead through progressive muscle relaxation for 5 minutes and then told to practice relaxing. At 4:55pm (the 40-minute timepoint), pre-test measures were taken. At 5pm, adolescents participated in the Trier Social Stress Test- child version (TSST-C [16]), as described below. The TSST-C procedure lasted 20 minutes. After the TSST-C, adolescents remained for an additional 60 minutes (from 5:20pm to 6:20pm) to examine recovery from exposure to the stressor. No instructions for relaxation were given during this period. Twenty minutes after the conclusion of the TSST-C (5:40pm), adolescents were debriefed regarding the TSST task. After the last assessment at 6:20pm, adolescents were disconnected from the heart rate and blood pressure devices.

2.5.2 TSST Procedure—The Trier Social Stress Test-Child version (TSST-C [16]) was used as a social stressor. The TSST-C was performed according to instructions provided by Buske-Kirschbaum and colleagues, except that in this study the adolescent prepared and delivered the speech in the same room (rather than a separate “preparation room”). At 5pm, two unfamiliar adults (the “judges”) enter the laboratory room and tell the adolescent that they will have to finish writing a story. They tell the adolescent to “make the story as exciting as possible” because they will be “competing against other teenagers.” The judges give the adolescent a story stem (used by Buske-Kirschbaum et al. [16]) and then leave the room. The research assistant collects self-reported emotion, cortisol, and HR/BP levels and then tells the adolescent to prepare the story for 5 minutes (from 5:05pm to 5:10pm). At 5:10pm, the judges re-enter the room. One judge places an audio-recorder in front of the adolescent and asks him/her to stand up and recite the story back for 5 minutes while he/she is videotaped and audio-taped. After the 5 minutes are finished, the second judge asks the adolescent to remain standing and complete a math task (“subtract the number 13 from 1023 over and over as quickly and accurately as possible”) for 5 minutes. The judges were trained research assistants. They were instructed to maintain a neutral expression and not to assist the adolescent during the tasks. During the speech and math tasks, the youth was asked to hold their arm/hand still so as to minimize movement effects on heart rate recordings.

The TSST is one of the most widely used social stress tasks in adults and children/adolescents [23,46]. The TSST has been found to elicit a robust activation of the HPA axis system [42], the sympathetic nervous system as assessed by heart rate and blood pressure [40], and emotional arousal as assessed by self-reported emotion [35] in children and adolescents. Furthermore, the TSST is a speech and math task, making it similar to events occurring in

adolescents' lives at school [44] and is a social-evaluative stressor, which may be particularly anxiety-provoking for adolescents [26].

2.6 Measures

2.6.1 HPA axis Response—Salivary cortisol levels were measured as a marker of HPA axis activation. Salivary cortisol measures free cortisol and is a well-established non-invasive measure of HPA axis functioning that correlates with plasma cortisol [43]. Saliva was collected using a cotton swab which participants were instructed to place between their tongue and cheek for approximately 2 minutes until the swab was completely saturated. Participants were asked to focus their gaze on a segment of lemon being squeezed two feet away from them in order to stimulate saliva flow. The saliva swab was then collected in a plastic tube, which was placed directly on ice and stored at -20C. Saliva samples were assayed in duplicate following standard radioimmunoassay kits with no modifications (Coat-A-Count Cortisol Kit, Diagnostic Products Corporation, Los Angeles, CA) at a University laboratory. The intra-assay coefficients of variation range from 3.0 to 5.1%.¹

Saliva samples were taken at pre-test (+40 minute timepoint), at “preparation” (+47, right before adolescent prepared the story), immediately after the speech and math tasks (+65), and every fifteen minutes through one hour of recovery (+80, +95, +110, +125). Cortisol levels were not able to be assayed due to an insufficient amount of saliva for three adolescents at one to three timepoints. These three participants are included in the main Linear Mixed Effects (LME) analyses, since they have data for at least two timepoints, but they were excluded from ANCOVA and regression analyses.¹

2.6.2 Self-reported emotion—Adolescents' self-rated anxiety was assessed using a 10-point visual analog scale in which 0 was anchored at “none at all” and 10 at “more than ever”. Participants rated how “tense, anxious and/or jittery” they felt in that moment.

Reports of other negative emotions (anger, sadness, and fear) were assessed with the Differential Emotions Scale-Revised short form (DES-R [37]). The present study used the anger, sadness, and fear subscales of the DES. Each subscale is made up of 5 adjectives describing the particular emotion state. The adolescent rates on a 5-point scale the extent to which each word describes the way he or she feels in the present moment. The DES shows good psychometric properties [37] and has been used with children and adolescents [11,19]. To further ensure validity of the DES, at the start of the session, the research assistant read each item to the adolescent aloud and defined any words that were unfamiliar to him/her.

Emotions were examined at pre-test (+40), preparation (+47), after the speech and math tasks (+65) and at 15 and 30 minutes after the speech and math tasks (+80, +95). Emotion was only examined through 30 minutes of recovery because emotional experiences are typically short-lived. In the present study, almost all participants had scores of zero on anxiety and negative emotion after the 30 minute recovery timepoint. Data was missing at one or two timepoints for three adolescents due to refusal to complete the anxiety scale and DES measures- these three are included in the main (LME) analyses, but not in ANCOVA or regression analyses.

2.6.3 Cardiovascular response—A Critikon Dinamap 120 Patient Monitor was used to assess systolic blood pressure (SBP) and diastolic blood pressure (DBP). A pulse sensor was attached to the participant's forefinger on their non-writing hand and was connected to the Dinamap Monitor to provide a measure of heart rate (HR). Blood pressure was measured at

¹Subjects with missing data were not different from those with complete data on any demographic variable, with one exception: Youth who were missing systolic blood pressure data were more likely to be NCE, have mother education less than high school level, and to be non-African-American.

pre-test (+40), at preparation (+47), after the speech and math tasks (+65), and at fifteen minutes of recovery (+80). Heart rate was measured at pre-test (+40), at preparation (+47), at two points during the speech and math tasks (+55, +60), after the tasks (+65), and at fifteen minutes of recovery (+80). HR and BP data were only examined through 15 minutes of recovery because cardiovascular responses are fast-acting and brief. SBP data was missing at one to three timepoints for three adolescents and DBP was missing at one to three timepoints for six adolescents- these youth are included in the main (LME) analyses, but not in ANCOVA or regression analyses. In addition, BP data was completely missing for three adolescents due to equipment malfunction. Those three are excluded from all blood pressure analyses. HR data was missing at one to three timepoints for seven adolescents- these seven are included in the main (LME) analyses, but not in ANCOVA or regression analyses.

2.7 Data Analysis Plan

2.7.1 Possible control variables—As stated above (In the *Laboratory stress session* section), medication use on the day of the laboratory session was included as a control variable in all analyses. In addition, we considered the following variables as potential control variables, because of their theorized relations with cocaine exposure status and stress response: race, mother education level, obstetric complications, and mother alcohol, tobacco, and marijuana use during pregnancy. For each variable, if it showed a cocaine exposure group difference or if it showed a significant or trend level ($p < .10$) relation with any stress response variable (tested in a separate Linear Mixed Effects models), it was included as a control variable. The following variables met this criteria: mother education level (PCE group difference, see Table 1), mother alcohol, tobacco, and marijuana use (PCE group difference, see Table 2), and obstetric complications (predicted cortisol and HR response, p 's $< .10$).

2.7.2 Stress response analyses—Linear Mixed Effect (LME [48]) models with compound symmetry covariance structures were used to analyze responses to the stressor, using the SPSS Mixed command. Linear mixed models are useful when there is missing data, as it prevents exclusion of subjects with missing data points [51]. The between-subjects factors were exposure group (PCE, NCE) and child gender (boy, girl) and the within-subjects factor was timepoint (varying levels). The model tested main effects of exposure group, child gender, and timepoint, and exposure group X timepoint, gender X timepoint, exposure group X gender, and exposure group X gender X timepoint interactions. If interactions between exposure group X gender and exposure group X gender X timepoint were not significant, they were dropped from the equation. Follow-up analyses were conducted using the COMPARE command within the mixed models analysis syntax. LME analyses controlled for mother education level, obstetric complications, mother alcohol, tobacco, and marijuana use in pregnancy, and adolescent medication use on the day of the lab session. Pre-test (“pre-test”) group, gender, and group X gender effects on variables were tested with ANCOVAs, controlling for the same control variables. In the case of pre-test differences for any particular measure, the LME model included the pre-test value of that measure as a covariate predicting response from the +47 (preparation) timepoint onward. Cortisol results were additionally analyzed with Area Under the Curve (AUC) analyses. The area under the curve was calculated with respect to ground [64]. ANCOVA analyses tested group, gender, and group X gender effects on AUC scores, controlling for the control variables.

Cohen's d effect sizes were calculated for significant ANCOVA results and from LME findings of group differences (from the F statistic). For Cohen's d statistics, .2 - .3 is considered a small, .4 a medium, and .8 or above a large effect.

2.7.3 Moderator analyses—Moderating effects of caregiver-child relationship quality were examined, following Baron and Kenny [7], by conducting LME analyses with exposure

group, timepoint, caregiver-child relationship quality, and exposure group X timepoint, relationship quality X timepoint, exposure group X relationship quality, and exposure group X relationship quality X timepoint interactions. Also, regression analyses were conducted to determine whether caregiver-child relationship quality moderated exposure group effects on pre-test measures, with exposure group, relationship quality, and group X relationship quality as predictor variables and pre-test scores on each outcome variables as the dependent variables. Moderator analyses included the control variables listed above. Significant interactions between exposure group and parent-child relationship quality indicate the presence of moderation.

3. Results

3.1 Data Inspection and Transformations

Data were examined for normality. For cortisol, there were eight outlier data points (> three standard deviations above the mean). These data points were reassigned a value equal to three standard deviations above the mean (similar procedures have been used in other studies of salivary cortisol [41,72]). For self-reported anger, sadness, and fear, variables were positively skewed and so square root transformations for these were used in analyses, although untransformed values are presented in figures for ease of interpretation.

3.2 Analyses of Pre-Stress Scores

As expected, main effects of exposure group or gender or exposure group X gender interactions were not observed at the pre-test timepoint (40 minute timepoint) for any variable, except systolic blood pressure (SBP). For SBP, there was a gender main effect ($F[1, 67] = 8.57, p = .01$, Cohen's $d = .62$), with boys higher than girls (for boys, $M = 116.97, SD = 13.22$; for girls, $M = 109.46, SD = 10.96$). LME analyses for SBP included pre-test SBP as a covariate.

3.3 Stress Response: Exposure Status and Gender Effects

3.3.1 Salivary cortisol—LME analyses showed a significant exposure group X timepoint interaction effect on salivary cortisol levels, $F(6, 468.05) = 2.99, p = .01$ (shown in Figure 1). Follow-up contrasts indicated that PCE adolescents had higher cortisol levels than NCE adolescents at the +40 (pre-test) timepoint ($F[1, 109.90] = 7.47, p = .01, d = .52$), the +47 (preparation) timepoint ($F[1, 109.42] = 7.64, p = .01, d = .54$), and the +125 (final recovery) timepoint ($F[1, 108.64] = 6.05, p = .02, d = .47$). Since the LME follow-ups showed significant pre-test differences (even though there were not pre-test differences in the ANCOVA analyses), LME analyses were re-run covarying pre-test cortisol levels. These results were similar, with a significant exposure group X timepoint interaction ($F[5, 381.39] = 2.94, p = .01$), with PCE greater than NCE at the +47 timepoint ($F[1, 110.66] = 5.55, p = .02, d = .45$) and at the +125 timepoint ($F[1, 110.66] = 4.00, p = .048, d = .39$).

There was also a significant main effect of exposure group ($F[1, 73.16] = 4.64, p = .04, d = .49$), with PCE greater than NCE in cortisol (for PCE group, $M = .19, SE = .02$; for NCE group, $M = .13, SE = .03$). There was also a main effect of timepoint ($F[6, 468.05] = 12.72, p < .0001$), with cortisol levels increasing 15 minutes after the stressor and then decreasing over the recovery timepoints.

Area Under the Curve (AUC) analyses showed similar findings (note that AUC analyses had a N of 81 because one subject had missing data at the final timepoint). A significant cocaine exposure group main effect was found ($F[1, 72] = 6.19, p = .02, d = .43$), with higher cortisol AUC scores in the PCE group ($M = .19, SE = .03$) than the NCE group ($M = .12, SE = .03$). In addition, a new main effect of gender emerged ($F[1, 72] = 4.76, p = .03, d = .27$), with higher cortisol AUC scores for boys ($M = .18, SE = .02$) than girls ($M = .13, SE = .03$).

3.3.2 Anxiety—LME analyses showed a significant exposure group X gender X timepoint interaction for self-reported anxiety, $F(5, 185.05) = 3.33, p = .01$ (shown in Figure 2). Follow-up contrasts indicated that, at the +65 timepoint (right after the stressor), PCE girls had significantly higher anxiety levels than NCE girls, $F(1, 108.23) = 6.34, p = .01, d = .49$, with no exposure group difference for boys. Also, NCE boys had higher anxiety than NCE girls, $F(1, 131.17) = 4.23, p = .04, d = .37$, with no gender difference for PCE adolescents. In addition to the interaction, there was a significant main effect of timepoint ($F[4, 308.22] = 11.61, p < .0001$), with anxiety increasing following stress and then decreasing over the recovery timepoints.

3.3.3 Anger—LME analyses showed a significant main effect of gender on anger, $F(1, 73.07) = 5.74, p = .02, d = .56$, with girls reporting higher anger than boys across timepoints. There was also a main effect of timepoint ($F[4, 308.22] = 11.61, p < .0001$), with anger increasing following stress and then decreasing over recovery.

3.3.4 Fear and sadness—There were no significant exposure group or gender main effects or interactions for self-reported fear and sadness. There were timepoint main effects for both variables (for fear, $F[4, 312.37] = 5.54, p < .0001$; for sadness, $F[4, 312.21] = 17.26, p < .0001$), with fear and sadness increasing following stress and then decreasing over the recovery timepoints.

3.3.5 Heart rate—LME analyses showed no significant main effects or interactions with exposure group or gender for heart rate. There was a significant main effect of timepoint ($F[5, 385.52] = 108.22, p < .0001$), with HR rising during the stressor and then decreasing through the recovery timepoint.

3.3.6 Blood pressure—After controlling for pre-test SBP (due to the gender difference in SBP at pre-test), there were no main effects or interactions with exposure group or gender for SBP. There was a timepoint main effect ($F[2, 144.33] = 18.10, p < .0001$), with SBP increasing after the stressor and then decreasing at the recovery timepoint.

For diastolic blood pressure (DBP), LME analyses showed two significant interactions. First, an exposure group X gender interaction was found ($F[1, 68.48] = 6.24, p = .02$), with follow-ups indicating that PCE boys had lower DBP than NCE boys ($F[1, 67.88] = 4.82, p = .03, d = .54$) with no exposure group difference for girls (see Figure 3). Second, an exposure group X timepoint interaction was found ($F[3, 216.58] = 3.68, p = .01$), with follow-ups indicating that PCE adolescents had lower DBP than NCE adolescents at the +80 (recovery) timepoint ($F[1, 122.81] = 4.45, p = .04, d = .39$) (see Figure 4). In addition to interactive effects, there was a significant main effect of timepoint on DBP ($F[3, 216.53] = 15.46, p < .0001$), with DBP increasing after the stressor and then decreasing at the recovery timepoint.

3.3.7 Effects of control variables—In addition to effects of PCE and gender, there were a few effects of the control variables on stress response. Mothers' marijuana use and less optimal obstetric conditions were associated with lower cortisol levels (p 's $< .05$) and mothers' alcohol use was associated with lower anger ($p = .03$).

3.4 Caregiving Quality as a Moderator

Interactions between exposure group and caregiver-child relationship quality as measured by caregiver report on the Parenting Stress Index were not significant for any outcome variable, indicating a lack of support for moderation. Unexpectedly, though, significant relationship quality X timepoint interactions emerged in the prediction of cortisol and self-reported anxiety. As follow-up, regression analyses were conducted at each timepoint, with relationship quality

as the predictor variable and the control variables included. Higher relationship quality scores (indicating *poorer* relationship quality) were associated with lower self-reported anxiety levels at the +65 timepoint (immediately after the stressor), $\beta = -.25$, $t(70) = -2.08$, $p = .04$. Follow-up regressions were not significant for the prediction of cortisol. The non-significant pattern of results was that higher (poorer) relationship quality was associated with lower cortisol levels after the stressor (e.g., $\beta = -.21$ at the +80 timepoint).

3.5 Secondary Analyses Pertaining to Adolescent Drug Use

Despite the request to refrain from drug use prior to the TSST session, 13 youth had positive urine screens (12 for marijuana and 1 for cocaine) on the laboratory day (with no positive alcohol breathalyzer screens). The incidence of positive urine screens did not differ by cocaine exposure group ($\chi^2 = 1.81$, *ns*). We conducted secondary analyses including urine screen (positive/negative) as a control variable and results were similar (all significant main effects/interactions remained significant), except that the interactions for diastolic blood pressure fell from significant to trend-level ($p < .10$).

4. Discussion

The present study is the first to examine stress response, and gender differences in this response, in prenatally cocaine and other drug exposed (PCE) and non-cocaine exposed (NCE) adolescents, who have been followed prospectively since birth. We found that PCE adolescents showed elevated HPA axis activation both at pre-test and one hour after stress exposure as compared to NCE youth. Cocaine exposure was also associated with self-reported anxiety and blood pressure response, although this differed by gender. PCE girls showed a pattern of high anxiety (relative to NCE girls) and high anger (relative to boys) in response to the stressor. Unexpectedly, PCE adolescents, particularly boys, showed lower diastolic blood pressure response to stress than NCE adolescents. These associations between prenatal cocaine and other drug exposure and emotional, neuroendocrine, and physiological response to stress were observed while controlling for maternal education, birth complications, mothers' other drug use in pregnancy, and child medication use and were not moderated by caregiver-child relationship quality (although relationship quality on its own predicted HPA axis and anxiety response). It should be noted that cocaine exposure "effects" discussed here may reflect interactive effects of cocaine with other drugs used in pregnancy, as well as post-natal environmental factors associated with parental drug abuse.

PCE adolescents' elevated cortisol levels before and after the stressor are consistent with findings from some studies of human infants that cocaine exposure is associated with increased cortisol at rest (64) and in response to stress ([25]), although one study with 11 year olds found reduced cortisol levels in response to stress [50]. Taken together with this prior research, the present study suggests that early alterations in HPA axis functioning may persist into adolescence in PCE youth. This could be due to an alteration in the developmental trajectory of HPA axis system ontogeny due to prenatal drug exposure, to the chronic stressful conditions often experienced throughout childhood and adolescence by children of drug abusing mothers, to a genetic transmission of HPA axis system disruption, or to a combination of these factors.

Notably, the present study found elevated cortisol levels for PCE youth before the stressor and also 60 minutes after the stressor. Cocaine exposure may be associated with hyperarousal of the HPA axis system at rest and the finding at one hour of follow-up may reflect that the adolescents had returned to their elevated "baseline" state. In other words, it may be that the exposure difference at one hour of follow-up is driven by the pre-stressor exposure difference. However, analyses were re-conducted covarying for pre-stressor cortisol levels and the exposure group difference at the 1 hour follow-up remained (although was weaker). Thus, it appears that PCE adolescents have a higher HPA axis set point at rest and are also higher in

recovery from stress over time. In order to more fully examine basal HPA axis functioning, future studies should examine HPA axis activity across a 24 hour period.

The finding of increased cortisol levels one hour after the stressor may suggest poor regulation of the HPA axis and in particular, altered glucocorticoid negative feedback and maintenance of increased CRF-HPA drive which could result in altered development of central stress circuits during adolescence [31]. Elevated cortisol levels at rest and in recovery from stress are a risk factor for the development of psychopathology in adolescence, particularly internalizing problems such as depression and anxiety [44,30,66].

The area under the curve analyses of cortisol response (but not the mixed effects model analyses) found a gender difference in cortisol response, with boys higher than girls. This is consistent with findings in adults with men showing a higher HPA axis response to stress than women [40].

In terms of adolescents' self-reported emotional response to stress, relations with cocaine exposure differed by gender. For anxiety, PCE girls showed the highest response, which was greater than NCE girls. Interestingly, NCE girls had the lowest anxiety response of all the groups and were lower than NCE boys. This is unusual, given that girls tend to report higher levels of "softer" emotions, such as anxiety, than boys (Brody, 1999). Future research would benefit from following-up this finding.

Girls (regardless of cocaine exposure status) showed a greater anger response to stress than boys. Although in dominant U.S. culture, girls are encouraged to limit anger displays, girls from low income environments (such as in the present study) may be encouraged to respond to social challenges with anger as a way to appear "tough" and to protect themselves in their neighborhood environments [15,60]. Combining the emotion findings, PCE girls show a pattern of both high anxiety and high anger, a pattern that could place them at risk for the development of psychopathology.

Findings for cardiovascular response to stress in the present study were mixed. No group or gender differences were found for heart rate. Boys showed greater systolic blood pressure (SBP) than girls, which is consistent with gender differences found in adulthood [3]. For diastolic blood pressure (DBP) response, PCE adolescents had a lower response than NCE youth. This is unusual given that the PCE adolescents showed an elevated stress response in terms of cortisol and (for girls) self-reported anxiety in the present study. It may be that PCE boys are showing under-arousal specifically in their cardiovascular response. This would be consistent with the finding that PCE boys (but not girls) show higher levels of externalizing disorders than non exposed children [21], disorders that are related to low levels of cardiovascular arousal [47].

The cocaine exposure group differences in stress responses, interestingly, were not moderated by caregiving quality. But, poorer caregiver-child relationship quality was related to lower anxiety in response to the stressor and to a pattern of lower cortisol. This is consistent with recent findings that poor caregiving may be associated with blunted stress response in children and adolescents [32] and that a negative home environment characterized by domestic violence is associated with blunted cortisol stress response in PCE children [50]. However, our finding should be interpreted with caution, given that we used a caregiver-report of the parent-child relationship, which may be limited by caregivers' social desirability concerns. Future research should follow-up this finding with multiple report and observational measures of caregiving and other aspects of the home environment (such as domestic violence).

4.1 Conclusions

In sum, the present study found differences between prenatally cocaine and other drug exposed and non cocaine exposed adolescents, both from low-income environments, in HPA axis response to a social stressor. Gender moderated relations between cocaine exposure status and other types of stress responses, including anxiety and blood pressure response. Group differences were found controlling for potential confounding variables including mothers' other drug use in pregnancy, mother education level, and obstetric complications. The study had some limitations. First, the sample included adolescents whose mothers consented to study participation and who have continued to participate across more than a decade. These women may not be as severely drug-using as the general population of cocaine abusers. However, even in this potentially less "at-risk" group, we still find significant PCE effects on stress response. Thus, we would presume that any effects in this study would be greater in the overall population of cocaine-using parents. Second, as mentioned above, our measure of caregiving was a self-report. Future studies should examine additional measures, such as direct observation of caregiving behaviors and of other aspects of home environment such as domestic violence as moderators of PCE "effects" on adolescent development. Third, our study had a relatively small sample size, which limited the power in particular to detect the PCE by caregiving interaction effects (since these included a continuous variable as a moderator). Future studies should examine interactions between PCE and home environment on stress response with larger samples.

Despite these limitations, the present study was the first prospective longitudinal study with humans of prenatal cocaine exposure and stress response in adolescence, an important period for the development of emotion regulation and the development of stress-related disorders. This study found elevated HPA axis arousal at baseline and one hour after a stressor in PCE adolescents as compared to NCE youth. Further, PCE girls showed particular risk in terms of emotional arousal to stress, with heightened anger and anxiety levels. The hyper-arousal of the HPA axis system in PCE youth may lead to the development of internalizing disorders. PCE girls may be particularly at risk for these disorders, given their heightened self-reported negative emotional arousal to stress, given that negative emotion has been linked to depression in youth [19]. In addition, PCE youth may cope with their heightened HPA axis arousal by using substances, which could lead to heightened risk for substance abuse. Although PCE adolescents did not show higher rates of substance use than NCE youth in this study during middle adolescence, they may show a greater progression to substance abuse as they enter late adolescence, a period of risk for substance use disorders. Future research should follow PCE youth into late adolescence/emerging adulthood to examine this hypothesis.

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Figure 1. Salivary Cortisol Response

Average salivary cortisol response over time to stress by cocaine exposure status

* Difference between Non Cocaine Exposed and Cocaine Exposed at $p < .05$.

Figure 2. Self-Reported Anxiety Response

Average anxiety response over time to stress by cocaine exposure status and gender

* Difference between NCE girls and PCE girls and NCE boys at $p < .05$.

Figure 3. Blood Pressure by Group

Average diastolic blood pressure across time by cocaine exposure status and gender

* Difference between NCE boys and PCE boys at $p < .05$.

Figure 4. Blood Pressure Response

Average diastolic blood pressure response over time to stress by cocaine exposure status

* Difference between Non Cocaine Exposed and Cocaine Exposed at $p < .05$.

Table 1

Demographic and birth status information for Prenatally Cocaine Exposed (PCE), and Non Cocaine Exposed (NCE) groups

	Non Cocaine Exposed <i>n</i> = 33	Cocaine Exposed <i>n</i> = 49	Test of drug group differences
Race: Number (%) in each group			$\chi^2(1, n = 82) = 1.83, ns$
African American	28 (84.8%)	46 (93.9%)	
Other	5 (15.2%)	3 (6.1%)	
Mother education: Number (%) completed high school	29 (87.9%)	30 (61.2%)	$\chi^2(1, n = 82) = 6.94^{**}$
Sex: Number (%) male	15 (45.5%)	25 (51.0%)	$\chi^2(1, n = 82) = .25, ns$
Child's Age : Mean (SD)	15.00 (.75)	14.91 (.86)	$t(80) = .44, ns$
Obstetric Complications Scale (OCS) ^a Score: Mean (SD)	92.39 (21.48)	84.05 (22.23)	$t(80) = 1.69, ns$
Parent-child relationship (PCR) ^b Score: Mean (SD)	1.72 (.76) (<i>n</i> = 32)	1.98 (.79) (<i>n</i> = 47)	$t(77) = -1.34, ns$

Note.

*
 $p < .05$,

**
 $p < .01$,

 $p < .001$,

ns indicates non significant.

^a Higher OCS scores indicate more optimal birth conditions.

^b Higher PCR scores indicate more negative parent-child relationship.

Table 2

Mothers' self reported substance use for Prenatally Cocaine Exposed (PCE) and Non Cocaine Exposed (NCE) groups

	Non Cocaine Exposed	Cocaine Exposed	Drug group differences?
<u>Substance Use in Pregnancy</u>			
Cocaine			
Days used out of 30: M (SD)	0	5.53 (5.54)	$U = 561.00$ ****
If used, # grams per day: M (SD)	N/A	.78 (1.47)	N/A
Alcohol			
Used alcohol: n (%)	15 (45.5%)	43 (87.8%)	$\chi^2 = 17.04$ ****
Days used out of 30: M (SD)	.45 (.51)	4.59 (7.19)	$U = 346.50$ ****
Tobacco			
Used tobacco: n (%)	6 (18.2%)	44 (89.8%)	$\chi^2 = 42.50$ ****
Days used out of 30: M (SD)	.18 (.39)	.88 (.39)	$U = 246.00$ ****
Marijuana			
Used marijuana: n (%)	3 (9.1%)	34 (69.4%)	$\chi^2 = 28.95$ ****
Days used out of 30: M (SD)	.09 (.29)	1.39 (4.25)	$U = 316.50$ ****

Note.

 $p < .0001$.

N/A indicates Not Applicable.

Categorical variables tested with a χ^2 .

Continuous variables tested with a Mann-Whitney U test due to non-normal distribution of data.