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Effects of prenatal cocaine exposure on infant reactivity and regulation

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Abstract

The purpose of this study was to examine the role of prenatal cocaine exposure and associated risk factors on infant reactivity and regulation at 7 months of infant age. Participants consisted of 167 mother-infant dyads participating in an ongoing longitudinal study of prenatal cocaine exposure, who completed the arm-restraint procedure at the 7-month assessment (87 cocaine exposed, 80 non-cocaine exposed). We hypothesized that cocaine exposed infants would display higher arousal or reactivity and lower regulation during a procedure designed to arouse anger/frustration. Results indicated that cocaine exposed infants were more reactive to increases in the level of stress from trial 1 to trial 2 but exhibited no change in the number of regulatory strategies as stress increased, unlike the control group infants. Infant birth weight moderated the association between cocaine exposure and infant regulation. Among cocaine exposed infants, those with lower birth weight displayed higher reactivity compared to those with higher birth weight. Contrary to expectations, there were no indirect effects between cocaine exposure and infant reactivity/regulation via environmental risk, parenting, or birth weight. Results are supportive of a teratological model of prenatal cocaine exposure for infant reactivity/regulation in infancy.

Keywords

Infant Regulation; Cocaine exposure; infant arousal

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1. Introduction

Recent studies and reviews of the consequences of prenatal cocaine exposure have noted that cocaine has subtle effects on areas that comprise the system responsible for emotional and behavioral regulation [52] [53]. Cocaine is known to inhibit the re-uptake of monoamines at the presynaptic junction, leading to higher concentrations of norepinephrine, serotonin, and dopamine in the synaptic cleft and higher levels of activation in the catecholaminergic systems [34] [57]. The regions of the brain that are rich in monoamines are the very centers involved in regulatory activities and reactivity to stress [52] [61] [76]. Thus, there has been growing concern that prenatal cocaine exposure may have consistent effects on the development of the regulatory system.

Indeed, a large number of studies have noted that prenatal cocaine exposure has been shown to increase risk for regulatory disturbances. For instance, cocaine exposed infants exhibit higher state lability, orienting, and attention problems in the neonatal period [22] [29] [44]. Studies beyond the neonatal period have indicated that cocaine exposure is likely to have lasting effects [6] [21][53] [66]. For instance, cocaine exposed infants demonstrated higher negative affect in response to novel stimulation or stress at 3–4 months of infant age [6] [53]. Others have reported similar associations between cocaine exposure and poor behavioral regulation during testing among 14 to 60 month old children [41]; higher impulsivity at 2 years of age [7]; higher frustration and more disruptive behavior during problem solving tasks among 4 year olds [25]; poor motor inhibition at 5 years [5]; and higher disruptive behaviors in the school setting [23] [24]. These behavioral data have been further supported by physiological data indicating that cocaine exposed infants showed increases in heart rate when presented with novel social stimulation compared to the more adaptive decrease in heart rate of control group infants [21]. Animal studies have noted that rat pups exposed to cocaine during gestation behave similarly to un-exposed pups under baseline conditions, but as the level of stress increases, they exhibit stress-induced freezing and increased levels of aggression [70] [79]. Thus, there is accumulating evidence that maternal cocaine use may have a negative impact on reactivity and regulation during affect-arousing or stressful situations. There is some indication from the animal literature that these differences may become more apparent as the level of environmental stress increases, although few human studies have specifically examined this issue. Indeed, only a handful of human studies [6] [7] [25] [56] [75] have used behavioral paradigms to examine cocaine effects on infant reactivity and emotion regulation during affect arousing situations in early infancy.

The major purpose of this study was to examine the impact of maternal cocaine use on the regulatory system in infancy. The regulatory system consists of two components: the latency and intensity of reactions to environmental stimulation (reactivity), and behavioral responses and strategies that would modulate these reactions (regulation). These two components may be measured by examining (1) the latency and intensity of an individual's reactions to affect arousing situations, and (2) the attentional or coping strategies used in response to such situations.

There is consensus in the literature that generally, regulatory strategies may be grouped into four broad domains, attentional strategies used to distract attention away from the affect arousing stimuli; self-comforting or self-soothing behaviors; approach-withdrawal behaviors; and intentional communicative behaviors [11] [45] [62] [71]. Developmental changes in the emergence and frequency of different regulatory strategies have been noted, with self-soothing behaviors being most common in early infancy and communicative strategies emerging later in infancy. Several studies have noted changes in expressions of negative affect or reactivity as a function of these putative regulatory behaviors [17] [71] [78].

Individual differences in both reactivity and regulation are thought to reflect the impact of a wide range of developmental influences. In addition to the potential teratological effect of cocaine on the regulatory system, maternal cocaine use is a marker variable for a number of other risk variables that may have a negative impact on the regulatory system [52]. These risk variables include other substance use, poor intrauterine growth, more negative parenting, and higher environmental risk. The majority of women who use cocaine also use heavier amounts of alcohol and cigarettes compared to non-cocaine using women. Alcohol and cigarettes are known to have significant teratological influences on regulatory processes [32] [33] [72]. Thus, the impact of maternal cocaine use can only be studied in the context of polydrug cocaine exposure and by measuring the use of other substances in addition to cocaine. Similarly, poor intrauterine growth is a factor that is consistently associated with both prenatal substance exposure and the regulatory system [1] [40] [59]. Poor fetal growth has been consistently associated with difficulties in regulating arousal and the development of self-regulatory strategies in infancy [26] [38] [51] [73], and poor behavioral regulation in later childhood [9] [77]. Thus, one pathway to regulatory difficulties among cocaine exposed infants may be via the impact of cocaine on fetal growth (e.g., low birth weight), and the association between poor fetal growth and poor behavioral regulation. In addition, as noted in previous studies of prenatal cocaine exposure [3], variables such as birth weight may also moderate risk, such that cocaine exposed infants with low birth weight (controlling for gestational age) may be most biologically vulnerable and at highest risk for poor developmental outcomes.

Apart from infant growth and other substance use, two primary risk factors related to cocaine use are negative parenting quality and greater environmental risk [46]. Cocaine using mothers have been reported to be more disengaged and passive during interactions with their infants or toddlers [37] [56], and to display lower responsiveness, and higher negative affect toward their infants [15] [16] [28]. These aspects of parenting behavior have direct implications for infants' reactivity and regulation in affect arousing situations. Parents play a critical role in helping children manage their arousal and keep distress within tolerable limits in infancy [30] [65] [74] by reading their children's emotional signals and responding with appropriate levels of soothing or stimulation. Parents who exhibit poor sensitivity to infant cues, high negative affect, and low warmth toward their infants are more likely to have infants who have difficulty regulating arousal in affect arousing situations. These aspects of parenting may also moderate risk.

Finally, cocaine exposed infants experience higher levels of environmental risk as indicated by a number of factors such as lower maternal education, single parenting, lack of a caregiving routine, instability in caregiving situations, multiple separations from the primary caregiver, unstable living arrangements, and lack of social support [4] [8] [14] [47] [60]. Several studies have noted the importance of examining the potential effects of these differences in the caregiving situation of cocaine exposed infants on developmental outcomes [4] [8] [14]. With a few exceptions [25] [58] [68], results from most studies indicate that environmental risk is an important predictor of negative child outcomes [4] [6] [8] [14] [31] [47] [67].

Based on this literature, we hypothesized that cocaine exposed infants would display higher arousal or reactivity and lower regulation during a procedure designed to arouse anger/frustration. We expected that group differences in reactivity and regulation would become more apparent from trial 1 to trial 2, tentatively assuming that the level of stress increased across the two trials. We also hypothesized that the association between prenatal cocaine exposure and infant reactivity or regulation may be indirect, via lower birth weight (controlling for gestational age), poor parenting, or higher environmental risk. We also examined birth weight, parenting, and environmental risk as potential moderators of the association between cocaine exposure and reactivity/regulation.

2. Methods

2.1 Participants

Participants consisted of 167 mother-infant dyads participating in an ongoing longitudinal study of prenatal cocaine exposure, who completed the arm-restraint procedure at the 7-month assessment (87 cocaine exposed, 80 non-cocaine exposed). Maternal interviews and infant assessments were conducted at 4–8 weeks and again at 7 months of infant age. An outreach worker on the project staff recruited all participants after delivery from two local area hospitals. Mothers ranged in age from 18 to 42 years ($M=29.78$; $SD=5.46$). The majority of mothers were African American (74%), were receiving Temporary Assistance for Needy Families (71%) at the time of their first laboratory visit (Years 2001–2004), and were single (60%). All families were recruited from the same hospital serving a predominantly low-income population and the two groups were matched on maternal age, education, maternal race/ethnicity, and infant gender. 46% of the infants were male. The study received approval from the institutional review boards of the hospitals as well as the primary institutions with which the authors are affiliated. Informed written consent was obtained from all recruited participants. Participants received \$35 at the 4–8 week assessment, and \$50 at the 7-month assessment in the form of gift certificates, checks, and infant toys for their participation. All assessments were conducted at age corrected for prematurity.

By 7 months of infant age, 17 infants in the cocaine group had been removed from parental care and placed in non-parental care. Of these 17 infants, 10 (59%) were in non-kin care, with the remainder being cared for by a grandmother or maternal aunt. All 7-month assessments were conducted with the primary caregiver of the child at that time, although for ease of presentation, the term mother or maternal is used throughout the paper when referring to the primary caregiver. The primary caregiver was identified as the adult who had legal guardianship of the child and accompanied the child at the 7 month appointment.

2.2 Procedure

All mothers were screened after delivery for initial eligibility and matching criteria. Exclusionary criteria for all mothers were (a) maternal age younger than 18 years, (b) use of illicit substances other than cocaine or marijuana, and (c) significant medical problems for the infant (e.g., genetic disorders, major perinatal complications, baby in critical care for over 48 hours). The two groups were matched on maternal age, race, education, and infant gender.

Interested and eligible mothers were given detailed information about the study and asked to sign consent forms. About 2 weeks after delivery, mothers were contacted and scheduled for their first laboratory visit, which took place at the time that their infant was approximately 4–8 weeks old. A second visit was scheduled when the infant was 7 months old. All visits consisted of a combination of maternal interviews, observations of mother-infant interactions, physiological and observational assessments of infant arousal and arousal regulation. In the circumstance of a change in custody arrangements, the person who had legal guardianship of the child was contacted and asked to participate. Biological mothers were interviewed at the 4–8 week assessment in order to obtain accurate information about prenatal substance use.

Once a family was recruited into the cocaine group, the closest matching non-cocaine group family was recruited. However, a significantly higher proportion of mothers in the non-cocaine group declined participation or withdrew before formal enrollment, resulting in a smaller number of families in the control group. Of the 4,800 women screened at delivery, 340 were eligible for participation in either group based on inclusion criteria and cocaine use. Of these 340 women, 35% either declined participation or were not enrolled in the study because they expressed initial interest but later withdrew. Of the 220 mother-infant dyads who completed

the 4- to 8- week laboratory visit, 7 declined to participate in the 7-month assessment or did not show up after repeated reschedules, 10 were unable to be located, 2 were dropped from the study (one because of a diagnosis of fetal alcohol syndrome, and another because of a diagnosis of Shaken Baby Syndrome), 5 were in the middle of new custody arrangements, and 7 mothers no longer had custody of their children and the foster parent was uninterested in participating. Of the 189 (86%) mother-infant dyads that completed the 7-month assessment, 22 (12%) did not participate in the behavioral assessments of infant reactivity and regulation due to the distress level of the child during the set up of the assessment, resulting in a final sample of 167 mother-infant dyads. There were no significant differences between families with complete vs. missing data at 7 months on any demographic or substance use variable. Approximately 60% of the infants with missing data on the reactivity/regulation paradigm were in the cocaine group, but this association (between missing data status and cocaine group status) was not significant.

2.3 Assessment of growth and risk status

Three measures of growth were used in this study: birth weight (gm), birth length (cm), and head circumference (cm). All measurements were taken by obstetrical nurses in the delivery room and recorded in the infant's medical chart. Research staff recorded this information from the charts after recruiting the mother-infant dyad. Medical chart review at the time of recruitment also was used to complete the Obstetrical Complications Scale (OCS) [48], a scale designed to assess the number of perinatal risk factors experienced by the infant. Higher numbers on this scale indicate a more optimal obstetric score.

2.4 Identification of Substance Use

Cocaine status was determined by a combination of maternal report, chart review, and maternal hair analysis. Urine toxicologies were routinely conducted at the first prenatal visit on maternal urine and/or at delivery (for those mothers who tested positive prenatally, obtained prenatal care elsewhere, or did not receive any prenatal care) on infant and maternal urine by participating hospitals. Urine toxicology results were available for 90% of the families in the control group and 92% of the families in the cocaine group. Mothers were included in the cocaine group if self-reports were positive, regardless of urine toxicology or hair-sample results. Similarly, mothers who reported that they did not use cocaine but had positive urine toxicology or hair samples were included in the cocaine group. Mothers were included in the control group if they did not test positive on urine or hair, and denied using cocaine during pregnancy based on self-report.

Urine toxicologies consisted of standard urine screening for drug level or metabolites of cocaine, opiates, benzodiazepines, and tetrahydrocannabinol. Urine was rated positive if the quantity of drug or metabolite was >300 g/ml, but were not confirmed by gas chromatography/mass spectrometry (GC/MS). Hair samples were collected from the mothers at the first laboratory visit and sent to the Psychomedics Corporation for radioimmunoanalyses (RIAH). Hair samples were screened for cocaine followed by a GC/MS confirmation for positive cocaine screens. Drugs and their metabolites are absorbed into the hair and can be extracted and measured. As hair grows at an average rate of 1/2 inch per month, it can record a pattern of drug consumption related to the amount and frequency of use [2]. Thus, a 2-inch length of hair could contain a record of approximately 4 months of use, and given adequate hair length (i.e., about 4–5 inches), use per trimester may be recorded. Drugs become detectable in hair about 3 to 4 days after use, a time when cocaine is rendered undetectable by urinalysis. RIAH is the most well-established hair-analysis technique and has been replicated by independent laboratories across the world [50]. GC/MS confirmations of RIAH have not revealed any false positives because of testing errors [50].

About 98% of the mothers in the cocaine group had positive hair or urine toxicologies, and 2% of mothers admitted having used cocaine in the brief self-report screening instrument administered after delivery, but did not have the hair or urine results. Mothers in the comparison group reported not having used any illicit substances other than marijuana and did not test positive for cocaine in urine or hair.

The Timeline Follow-Back Interview (TLFB) [69] was used to assess maternal substance use before, during, and after pregnancy at the 1 month visit and in the previous 6 months at the 7 month visit. Participants were provided a calendar and asked to identify events of personal interest (i.e., holidays, birthdays, vacations, etc.) as anchor points to aid recall. This method has been established as a reliable and valid method of obtaining longitudinal data on substance-use patterns, has good test-retest reliability, and is highly correlated with other intensive self-report measures [10] [13]. The TLFB yielded data about the average number of days of cocaine use per week, average number of joints smoked per week, average number of cigarettes smoked per week, and average number of standard drinks per week, for each trimester of pregnancy and for the postnatal period.

Cocaine use ranged from 0 to 6 days of cocaine use per week of pregnancy. Self-reported cocaine use decreased substantially over the duration of pregnancy from approximately once a week in the first trimester to once a month in the third trimester, although only 5 women reported use only in the 1st trimester. The remainder of the women who reported using cocaine reported use throughout pregnancy. The majority of the women in the cocaine group used crack cocaine.

2.5 Infant Reactivity and Regulation

Infant reactivity and regulation was assessed using an anger/frustration paradigm [36] [71]. In this paradigm, infants are allowed to play with an attractive toy for 15–30 seconds while seated in a high chair. The caregiver is asked to stand behind the child. Once the child is engaged in the toy, the caregiver is asked to place her hands on the child's forearms, move them to the child's sides, and hold them there for 30 seconds, while maintaining a neutral expression. After the first trial, the caregiver is again asked to engage the child with the toy for 30 seconds followed by a second 30-second trial. The session is stopped if the child reaches a maximum distress code, defined as the child reaching the highest intensity of negative affect of a full cry or at the caregiver's request. This occurred for 8 infants (5 nonexposed and 3 exposed), and following the Laboratory Temperament Assessment Battery (LabTAB) manual (see below), these children were assigned the maximum distress code for the remainder of the session. The child was allowed to play with the toy at the end of the two trials.

A series of behavioral measures were used to assess reactivity and regulation. Each of the two 30-second trials of the arm restraint procedure was divided up into six 5-second epochs. For the behavioral coding of reactivity, four measures were derived from the arm restraint episode. Two were derived from scoring facial expressions of anger and sadness using the guidelines of the LabTAB Manual, developed by Goldsmith and Rothbart [35]. For each 5-second epoch, peak intensity of anger facial expressions and peak intensity of sadness expressions were scored. The intensity of affect expression was scored using Affex [43], adapted from Izard's Maximally Discriminative Facial Movement Coding System (1979). Ratings ranged from 0 to 3, with higher scores indicating higher intensity of negative affect. The affect expression scores for each 5-second epoch were averaged for each trial in order to create two composite scores for each trial, reflecting average intensity of anger and sadness for trial 1 and trial 2. Higher scores indicated higher arousal or reactivity. In addition to expressions of negative affect, we also coded latency to anger ($M=16.78$ and 13.31 , $SD=12.05$ and 12.29 for trials 1 and 2 respectively) and sadness ($M=15.77$ and 12.53 , $SD=11.91$ and 12.26 for trials 1 and 2

respectively) in each trial as two additional indicators of reactivity. Latency scores ranged from 0 to 30 for each trial, with higher scores indicating longer latencies and lower reactivity.

For the behavioral coding of regulation, infant behaviors reflecting attentional strategies, struggle to escape (often called avoidance in previous studies), self-comforting, tension release, and communication attempts were coded per second during the arm restraint, based on prior research [11] [17] [71]. Attentional strategies were coded when the infant directed attention away from the attractive toy, looking at the mother, the examiner, or the environment. Struggle to escape was coded when the infant arched his/her back attempting to escape or struggled against the restraint. Self-comforting behaviors included repetitive motor actions or sucking. Tension release included high intensity or frequent gross motor movements. Finally, communication attempts included gestures or non-negative vocalizations [71]. The number of seconds each behavior was observed during each 5-second epoch was the measure of regulatory behavior. In addition, as with measures of reactivity, the average duration of each regulatory behavior for each trial was computed. Finally, following previous studies [17], we computed a measure reflecting the number of different regulatory strategies used by the infant within each 5-second epoch and within each trial. Analyses of the distributional properties of the regulatory behaviors indicated that self-comforting and communication attempts were used quite infrequently, probably due to the context of arm restraint, and were not used in further analyses. Two coders blind to all information about the families coded both reactivity and regulation. Inter-rater reliability was calculated for 14% of the tapes. The inter-rater reliability for intensity of anger and sadness ranged from 89% to 90% across the 5-second epochs (Cohen's kappa value of $\kappa = .68$ and $.70$) and from 90% to 92% across the two trials ($\kappa = .69$ and $.74$). Similarly, inter-rater reliability for latency to anger and sadness ranged from 97% to 99% ($\kappa = .94$ and $.95$). The inter-rater reliability for regulatory behaviors ranged from 85% to 98% (κ ranged from $.60$ to $.95$) for the specific regulatory strategies and 95% to 98% (κ ranged from $.91$ to $.96$) for the number of different regulatory strategies across the 5-second epochs. Infant baseline state for the 30 seconds before arm restraint was coded from 1 to 6 [12]: 1-quiet sleep, 2-active sleep, 3-drowsy, 4-quiet alert, 5-active alert, and 6-fussing/crying.

2.6 Parenting

Parenting was assessed using behavioral observations during a Free Play task. Mothers were asked to interact with their infants as they normally would at home for 5 minutes in a room filled with toys. These interactions were coded using a collection of global 5-point rating scales developed by Clark, Musick, Scott, and Klehr [20], with higher scores indicating more positive affect or behavior. These scales have been found to be applicable for children ranging in age from 2 months to 5 years [19] [20]. Three composite scales of maternal behavior were derived from these items, positive involvement, negative affect, and sensitivity. These scales had high internal consistencies with Cronbach's alpha ranging from $.87$ to $.91$. High scores on all three dimensions are positive, so that high scores on negative affect indicates low negative affect.

Two coders rated parental behavior. Both coders were trained on the Clark scales by the first author and were unaware of group membership. The interrater reliability was conducted on a random selection of 14% ($n = 24$) of the tapes and was fairly high, ranging from Intraclass correlation coefficients of $r = .86$ to $r = .92$ for the three composite scales.

2.7 Environmental Risk

Following previous studies [4] [64], an environmental risk score was computed from measures administered at 7 months of infant age. This score was a composite of maternal race (non-White = higher risk), education (less than high school degree or GED = higher risk), single parent status, unstable living arrangements (living with friends or in a shelter), lack of close friendships or support for the primary caregiver (taken from the Addictions Severity Index)

[55], and a number of items administered as part of the Structured Clinical Interview [60]. These items included lack of male caregiver involvement, lack of a caregiving (sleeping, bathing, etc.) routine, no routine medical care, and prolonged and/or frequent separations from the primary caregiver. Environmental risk scores for the sample as a whole ranged from 0 to 8 ($M = 3.65$, $SD = 1.55$).

3. Results

3.1 Demographics and infant growth outcomes

Results from MANOVA with the demographic variables as the dependent measures and group status yielded a significant multivariate effect of group status, $F(3, 163) = 6.05$, $p < .01$. Results from univariate analyses indicated that control group mothers were younger, had lower parity, and higher education compared to those in the cocaine group, although the effect sizes were generally small (see Table 1). Partial correlations controlling for infant baseline state were computed to examine associations between demographics and the measures of reactivity and regulation at the two trials. There were no significant associations between any of the demographic measures and infant reactivity or regulation. Thus, none of the demographic variables were considered for further analyses. A second MANOVA was conducted with infant birth outcomes as the dependent measures. Results indicated a significant effect of group status on infant birth outcomes, $F(5, 161) = 8.11$, $p < .001$. Univariate analyses indicated that cocaine exposed infants had lower gestational age, birth weight, birth length, and cocaine using mothers had less optimal scores on the obstetrical complications scale compared to those in the control group (see Table 1). 87% of the cocaine exposed and 97% of the comparison infants (Pearson chi-square = 6.75, $p < .01$) were full term (≥ 37 weeks gestational age).

3.2 Maternal Substance Use

Results from MANOVA with prenatal substance use variables as the dependent measures and group status as the independent variable yielded a significant multivariate effect of group status, $F(4, 162) = 14.32$, $p < .001$. As expected, mothers in the cocaine group were heavier users of cigarettes, alcohol, and cocaine during pregnancy (see Table 2). There was no group difference in marijuana use. Results of MANOVA with postnatal substance use measures at 7 months yielded a significant effect of group status, $F(4, 162) = 7.62$, $p < .001$. Mothers in the cocaine group continued to be heavier users of alcohol, cigarettes, and cocaine, but not marijuana, during the postnatal period (see Table 2). Correlational analyses were conducted to examine associations between substance use and the measures of reactivity and regulation. There were no significant associations between any of the prenatal substance use measures (other than cocaine) or any of the postnatal substance use measures and infant reactivity or regulation. However, because of strong theoretical associations between other substance use and infant reactivity and regulation and the nested nature of maternal substance use during pregnancy, all remaining analyses including model testing were conducted with other substance use as covariates.

3.3 Parenting

Results from MANOVA with group status as the independent variable, and the three maternal behavior variables as dependent measures yielded a significant multivariate effect of group status, $F(3, 163) = 4.30$, $p < .001$. Univariate analyses indicated that mothers in the cocaine group displayed lower positive involvement and higher negative affect compared to those in the control group (see Table 2). These results remained unchanged when the 17 foster care mothers were excluded from the analyses.

3.4 Reactivity

The next step was to examine associations between cocaine group status and the four measures of reactivity at the two trials. Results from repeated measures MANCOVA with the four measures as the dependent variables, trial as the within subjects factor, other pregnancy substance use and baseline state as covariates, and group status as the independent variable, yielded a significant multivariate interaction of group by trial on reactivity, $F(4, 158) = 2.63$, $p < .05$. Univariate analyses indicated marginal interaction effect of group by trial on latency to anger $F(1, 161) = 3.72$, $p < .05$. Cocaine exposed infants exhibited decreases in latency to anger from trial 1 to trial 2, while infants in the control group did not (see Figure 1).

3.5 Regulation

Results from repeated measures ANCOVA with group status as the between subjects factor, other pregnancy substance use and baseline state as the covariates, trial (1 and 2) as the within subjects factor, and average number of regulatory strategies as the dependent variable, yielded a significant interaction effect of trial by group status, $F(1, 161) = 4.34$, $p < .05$. Analyses of simple effects indicated that cocaine group infants did not change in number of regulatory strategies from trial 1 to trial 2, but there was a significant increase in number of regulatory strategies among control group infants. There was no group difference in the average number of different regulatory strategies used in trial 1, but cocaine exposed infants used fewer regulatory strategies during trial 2 compared to those in the control group (see Figure 2). Among specific regulatory strategies, attentional strategies, tension reduction, and struggle to escape were used in further analyses. Communication and self-soothing strategies were not used frequently and were extremely skewed. Repeated measures MANCOVA with average duration of the three specific regulatory strategies as the dependent variables, other pregnancy substance use and baseline state as covariates, and trial as the within subjects factor, yielded no significant multivariate or univariate effect on group or interaction of group by trial on specific regulatory strategies. Thus, no further analyses were conducted with specific regulatory strategies as the dependent variables.

3.6 Indirect Pathways

Three sets of variables were originally considered for examination of indirect effects. These were low birth weight, parenting, and the measure of environmental risk. Only environmental risk was significantly correlated with number of different regulatory strategies in trial 1 ($r = -.16$, $p < .05$). Higher environmental risk was associated with lower number of regulatory strategies in trial 1. None of the other variables were associated with infant reactivity or regulation.

The significance of the indirect effect via environmental risk was examined using the indirect effect testing described by MacKinnon and colleagues [49]. The first step in estimating indirect effects was to estimate the association between cocaine group status and environmental risk. Linear Regression was used with environmental risk as the criterion variable and the dummy coded cocaine exposure status as the predictor. As indicated in Table 2, cocaine exposed infants experienced higher environmental risk ($\beta = .19$, $p < .01$). In the next step, the association between environmental risk and number of different regulatory strategies in trial 1 was estimated. Hierarchical Linear Regression was used with regulatory strategies as the criterion variable. Baseline status and other substance use during pregnancy were entered in the first step, the dummy coded cocaine exposure variable was entered in the second step, followed by the environmental risk variable in the third step. This model explained 7% of the variance in infant regulation. The asymmetric distribution of the product test was used to calculate the significance of the indirect effect [49]. The significance of the indirect effect was tested by dividing the estimate of the indirect effect by its standard error [49]. This yielded a z score of

-1.89, $p > .05$. Thus, the indirect effect from prenatal cocaine exposure to infant regulation via environmental risk was non-significant.

3.7 Interaction Effects

The next step was to consider if there was an interaction effect of birth weight, parenting, or environmental risk and cocaine group status on infant reactivity and regulation. Median splits were used to create high and low levels on the moderator variables. Repeated measures ANCOVA were used to examine if parenting, environmental risk or birth weight moderated the association between cocaine group status and infant reactivity and regulation. Prenatal substance use variables, baseline state, and gestational age were used as covariates. Results indicated a significant interaction of cocaine exposure and birth weight on latency, $F(1, 158) = 6.57$, $p < .01$, and intensity, $F(1, 158) = 9.46$, $p < .01$. Among exposed infants, those with lower birth weight (less than 3126 grams) had higher intensity and lower latency to anger (see Figure 3)¹ compared to those with higher birth weight.

4. Discussion

The primary goal of this study was to examine if prenatal cocaine exposure increased infant risk for higher reactivity and lower regulatory behavior, and if group differences became more apparent in trial 2, when presumably the level of stress increased. In general, results indicated that non-cocaine exposed infants tended to be relatively stable in the level of arousal or reactivity they exhibited across the two trials, while those exposed to cocaine responded with negative affect (anger and sadness) more quickly as the level of stress increased (trial 1 to trial 2). The opposite was true for number of regulatory strategies. Cocaine exposed infants did not change in the number of different regulatory strategies they used from trial 1 to trial 2, but infants not exposed to cocaine increased the number of different regulatory strategies they used with increasing levels of stress. These results indicate that cocaine exposed infants were more reactive to increases in the level of stress but did not increase the number of regulatory strategies as stress increased.

The results are supported by previous studies in both the animal and human literature, although few human studies have examined changes in arousal or reactivity and regulation among cocaine exposed infants beyond the neonatal period, using affect arousing situations that are not confounded by the quality of the mother-infant relationship (as in a still-face paradigm). In the animal literature, Spear and colleagues [70] noted that rat pups exposed to cocaine prenatally exhibited increased sensitivity to environmental stress by exhibiting stress-induced immobility and increased levels of aggression compared to controls or pups that experienced nutritional deficiency. The authors suggested that teratologic differences that may not be apparent under baseline conditions or lower levels of stress become more apparent as levels of stress increase. This theme has been echoed in human findings, as reflected in data indicating that cocaine exposed 3 month old infants exhibited greater irritability and crying during habituation procedures [54], more negative expressions during the re-engagement phase of the still-face paradigm at 4 months [6], and more negative interchanges and more negative affect matching with mothers during the still-face paradigm at 4 months [75]. In one of the few studies of reactivity and regulation among cocaine exposed 4 year olds, using a behavioral paradigm other than the still-face, Dennis et al. [25] reported that cocaine exposed boys were quicker to react with frustration (higher reactivity) and displayed more disruptive behaviors during a problem solving task compared to cocaine exposed girls, or those not exposed to cocaine. Thus,

¹All analyses were repeated with foster care status as a covariate. Results remained unchanged. Thus, the original analyses without using foster care status as a covariate are reported throughout the paper.

these results add to a growing body of literature indicating potentially specific effects of cocaine on the regulatory system.

Contrary to expectations, there were no indirect associations between prenatal cocaine exposure and reactivity or regulation. Of the relevant variables that we tested (birth weight, parenting, environmental risk), none were predictive of infant reactivity or regulation. Maternal cocaine use was associated with poor infant birth outcomes, as in all other cohorts of cocaine exposed infants [14] [42] [47]. Cocaine using mothers also smoked more cigarettes and consumed more alcohol during pregnancy, a result supported by virtually all other cohorts of cocaine using mothers. Finally, mothers in the cocaine group displayed lower positive involvement and higher negative affect compared to those not using cocaine. However, contrary to expectations, other substance use or maternal parenting behaviors were not related to infant reactivity or regulation. These results are generally supportive of a teratological model of prenatal cocaine exposure. Perhaps indirect or mediational effects will become more apparent with time, as the children increase in age and environmental factors continue to exert a significant effect on developmental changes in the regulatory system.

Although maternal behavior during play was not associated with infant reactivity or regulation, higher environmental risk was associated with lower number of regulatory strategies. However, the indirect association between prenatal cocaine exposure and number of regulatory strategies in trial 1, via environmental risk was non-significant. The association between environmental risk and regulatory strategies may explain the association between environmental risk and other aspects of child behavior found in older cohorts of cocaine exposed children. For instance, environmental risk was predictive of children's externalizing behavior, IQ, impulse control, and aggression in previous samples of preschool to school aged cocaine exposed children [4] [7]. The environmental risk variable included a number of different indicators of risk. Thus, it is difficult to isolate the specific aspects of risk that may be predictive of regulation. However, given the nested nature of risk characteristics among these high risk children, it is difficult to isolate a specific risk characteristic that may be more or less predictive of child outcomes.

Although infant growth was not predictive of reactivity or regulation, there was a significant interaction of cocaine exposure and infant birth weight on latency to anger. Cocaine exposed infants with lower birth weight exhibited lower latency and higher intensity of anger compared to those with higher birth weight. Thus, lower birth weight seems to increase risk and higher birth weight promotes resilience with regard to the regulatory system. It is important to note that because median splits were used in this study, the cut off for lower birth weight used in the study is sample specific and does not correspond to the standard definition of low birth weight. Few previous studies of prenatal cocaine exposure have examined factors that may increase risk or promote resilience when infant regulatory system is the outcome variable of interest. However, several studies have examined birth weight as a moderator of cognitive or language outcomes among cocaine exposed children. For instance, Beeghly et al. [3] reported a significant interaction of cocaine exposure and birth weight on language development, such that at the 10th percentile for birth weight, children with prenatal cocaine exposure had significantly lower language scores compared to those not exposed to cocaine. A similar interaction effect of exposure status and birth weight has been reported for psychomotor development as well [31]. The current results add to these studies, indicating that birth weight moderates risk for regulatory outcomes as well.

One caveat to the current results that is important to consider is that infants were limited in the types of regulatory strategies they could use in this laboratory paradigm because restraint was used to elicit anger. Because of the context, infants were not able to use strategies that may be effective in other naturalistic contexts where there is less control, such as approach and withdrawal. As noted by previous researchers [17], emotion regulation in structured laboratory

situations may be quite different from those in natural situations such as homes and daycare settings. However, one strength of these data is that they are objective and not dependent upon parent's perceptions of infant reactivity and regulation, or behaviors measured in the context of parent-child interactions such as the Still-Face.

This study has several limitations, in addition to those mentioned previously. First, accurate assessment of substance use both prenatally and postnatally is difficult. Pregnant and postpartum women are often hesitant to divulge substance use information, particularly illicit substances such as cocaine. One strength of this study is the use of multiple methods to ascertain prenatal substance use which partially mitigated this limitation even though the urine toxicology information was abstracted from medical records. However, measures of prenatal use were retrospective and measures of postnatal substance use were based on self-report alone. A second limitation is that the measure of maternal parenting behavior was brief, and limited to a single play session. However, this was an objective measure of parenting, as opposed to parent reports of their own parenting behavior. Additionally, previous studies have reported that affect synchrony is an important construct to consider as a predictor of infant reactivity and regulation [30]. It is possible that future studies that specifically assess affect synchrony during mother-infant interactions may report a different pattern of results. This is particularly critical given the lack of hypothesized associations between maternal behavior and infant reactivity and regulation. A third limitation of this study is the assumption that changes from trial 1 to trial 2 of the arm restraint reflects responses to increases in the level of stress. An interpretation of the current findings may be that cocaine exposed infants responded with higher arousal, perhaps experiencing greater stress in trial 2 compared to trial 1, while control group infants did not experience an increase in stress from trial 1 to trial 2. These results need to be interpreted with caution until replicated with other samples, using other anger/frustration paradigms. Finally, the results may be generalized only to infants exposed to crack cocaine, as the majority of the women used this form of cocaine during pregnancy.

Despite these limitations, these findings are important because they lend further empirical support to a growing body of literature documenting significant effects of prenatal cocaine exposure on the regulatory system, beyond the neonatal period. The use of a behavioral paradigm and examination of indirect and moderating factors are strengths of this study, although the paradigm was limited due to both the time (two 30 second intervals) and the context (arm restraint). The results are supportive of a teratological model of prenatal cocaine exposure on infant regulation, at least at 7 months of infant age. Results also highlight the role of infant birth weight as a moderator of risk.

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Figure 1.
Group by trial interaction effect on latency to anger.

Figure 2.
Group by trial interaction effect on number of regulatory strategies.

Figure 3.
Group by birth weight interaction effect on latency to anger. Bwt: birth weight.

Table 1
Group Differences in Demographic Variables and Birth Outcomes

Variables	M	Non-Cocaine SD	M	Cocaine SD	F value	η^2
<u>Demographics:</u>						
BM Age	28.57	5.60	30.99	6.05	7.13**	.04
BM Parity	3.28	1.66	4.25	2.27	9.93**	.06
Years Education	12.26	1.85	11.62	1.93	4.78*	.03
<u>Birth Outcomes</u>						
Gestational Age	39.33	1.27	38.68	1.83	6.91*	.04
Birth weight	3320.15	494.58	2988.85	523.81	17.58**	.10
Birth length	49.83	2.90	48.29	3.12	10.81**	.06
Head circumference	35.55	1.28	33.25	2.18	1.14	.007
OCS	100.53	17.15	86.38	16.18	30.07**	.15

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

Note. No correlation between birth outcomes and anger reactivity or # of regulatory strategies.

η^2 Partial eta square is a measure of effect size and reflects the proportion of total variance attributed to an effect. BM: Biological Mother; OCS: Obstetrical Complications Scale.

Table 2
Group Differences in Maternal Substance Use and Parenting Variables.

Variables	<u>M</u>	<u>Non-Cocaine</u> <u>SD</u>	<u>M</u>	<u>Cocaine</u> <u>SD</u>	F value	Partial eta sq.
Pregnancy:						
Cigarettes/week	9.81	21.91	36.26	42.04	35.62**	.18
Drinks/week	.06	.15	5.06	13.27	20.59**	.11
Joints/week	1.12	6.20	1.55	4.62	2.34	.01
Days cocaine/week	0	0	.94	1.58	28.46**	.15
Postnatal						
Cigarettes/week	14.52	28.81	36.57	42.75	19.63**	.11
Drinks/week	.39	.69	1.98	5.37	6.84**	.04
Joints/week	1.20	4.53	1.15	4.69	.01	.00
Days cocaine/week	0	0	.10	.37	11.78**	.07
Parenting						
Positive Involvement	3.90	.88	3.53	.96	6.25**	.04
Negative Affect	4.77	.39	4.53	.68	6.72**	.04
Sensitivity	4.21	1.05	3.97	1.09	2.00**	.01
Environmental Risk	3.35	1.67	3.93	1.38	6.05	.04

Note. High scores on Negative Affect indicate low negative affect. η^2 Partial eta square is a measure of effect size and reflects the proportion of total variance attributed to an effect.

*
 $p < .05$

**
 $p < .01$