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The Association Between Maternal Cocaine Use During Pregnancy and Physiological Regulation in 4- to 8-Week-Old Infants: An Examination of Possible Mediators and Moderators

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Abstract

Objective—To examine the association between maternal cocaine use during pregnancy and physiological measures of regulation, which included heart rate (HR) and respiratory sinus arrhythmia (RSA).

Methods—Potential mediators and moderators of this association were explored. Participants were 141 mother–infant dyads (77 cocaine exposed and 64 nonexposed) recruited at birth. Average infant HR and RSA was assessed at 4–8 weeks of age during a 15 minute period of sleep.

Results—Results indicated a dose-dependent effect of prenatal exposure to cocaine on RSA. There was no evidence that fetal growth or other prenatal exposure to substances mediated this association or that fetal growth or maternal age moderated this association. Regression analyses also indicated that birth weight (BW), but not birthlength (BL), head circumference (HC) or other substance use, mediated the association between prenatal exposure to cocaine and heart rate.

Conclusions—These results suggest that cocaine exposure is associated with physiological regulation at 4–8 weeks of age and highlight the importance of considering level of exposure when assessing infant outcomes.

Keywords

heart rate; prenatal cocaine exposure; regulation; respiratory sinus arrhythmia

The impact of maternal cocaine use during pregnancy on infant development has been widely researched during the past two decades. Many investigators have focused on the possible physical and cognitive effects of prenatal exposure to cocaine on the development of infants and young children. The findings of studies examining potential cognitive outcomes among cocaine-exposed children have been mixed and somewhat inconsistent (Lester, LaGasse, & Brunner, 1997) with recent reviews and meta-analyses suggesting that cocaine's effects on these outcomes may be subtle (Lester, LaGasse, & Seifer 1998). At the same time, there is increasing recognition that cocaine may have significant influences on regulatory behaviors. For instance, in their review, Lester et al. (1997) reported that of 9 studies focusing on regulatory processes among cocaine-exposed infants, seven reported

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significant group differences. These regulatory difficulties include poorer state regulation, increased arousal from sleep, and differential physiological responding to sensory challenges, as measured by both heart rate (HR) and cortisol levels, beginning in the neonatal period and persisting throughout the first year of life (Bendersky & Lewis, 1998a,b; Brown, Bakeman, & Coles, 1998; DiPietro, Suess, Wheeler, Smouse, & Newlin, 1995; Gingras et al., 1995; Karmel & Gardner, 1996; Mayes, Bornstein, Chawarska, & Granger, 1995; Mayes, Bornstein, Chawarska, & Granger, 1996; Regalado, Schechtman, Del Angel, & Bean, 1995; Regalado, Schechtman, Del Angel, & Bean, 1996). These findings are particularly significant when considering the fact that achievement of self-regulation is an important precursor to normal development. In fact, managing arousal in order to respond appropriately to environmental demands is among the earliest skills to develop during infancy. Thus, problems in this area may have implications for later functioning.

Although prenatal exposure to cocaine has increasingly been linked to poorer regulation during infancy, the association between prenatal exposure to cocaine and infant regulatory processes may not always be simple or direct. Arousal and regulatory processes during infancy are complex developmental phenomena that are influenced by a variety of endogenous and exogenous factors. In fact, the neural regulation of autonomic functioning is sensitive to a range of perinatal factors that may disrupt the development of self-regulatory skills (Porges, 1996) including a range of substances used during pregnancy as well as other infant and maternal risk variables. For example, heart rate (HR) is believed to reflect autonomic function and neurological integrity in young infants. Specifically, HR is predictive of later cognitive development and may impact reactivity to external stressors. An elevated resting HR is indicative of a higher level of physiological arousal which impacts both the quality and quantity of infant responsiveness to stimulation. Infants who are more highly aroused prefer less intense stimulation (e.g., Karmel, Gardner, & Magnano, 1991). Because an infant's approach toward or withdrawal from stimulation may reflect the infant's attempts to regulate its own level of arousal, HR functions as an important index of physiological regulation during early infancy.

In addition, respiratory sinus arrhythmia (RSA), which is a measure of heart rate variability (HRV) is thought to be an important physiological marker of regulatory control and has been considered an index of the capacity to self-regulate (Porges, 1991). Numerous studies have shown RSA during early infancy to be predictive of behavioral measures of regulation later in infancy and into childhood. For example, higher RSA is related to better emotional regulation (Stifter, Spinrad, & Braungart-Rieker, 1999) and easier soothing (Huffman et al., 1998). Thus, these measures may be particularly useful indices of the impact that prenatal exposure to cocaine has on regulation during early infancy. Obtaining these measures of physiological regulation during periods of minimal stimulation from the external environment is particularly relevant during early infancy. According to Porges (1996), competence in maintaining homeostasis by regulating autonomic processes such as temperature, respiration, blood pressure, and sleep is critical for numerous aspects of development including emotional and social development. Furthermore, measures of HR and HRV are state dependent. For example, RSA is most pronounced during quiet sleep (Katona & Jih, 1975; Schechtman, Harper, & Kluge, 1989).

Existing studies on the association between HR measures and maternal use of cocaine during pregnancy, however, have conflicting results. A few studies have found lower HRs(Silvestri, Long, Weese-Mayer, & Barkov, 1991), greater high-frequency power as a portion of total spectral power in cocaine-exposed neonates (Mehta et al., 1993) and greater overall HRV (Regalado et al., 1996; Regalado, Schechtman, Khoo, & Bean, 2001) in cocaine-exposed neonates. These studies suggest enhanced parasympathetic activity in cocaine-exposed neonates. Conversely, other studies have not found any effects of maternal

cocaine use on baseline HR or HRV during sleep among neonates (DiPietro et al., 1995; Mehta et al., 1993). However, these studies only examined the possibility of a direct, teratogenic effect of cocaine exposure on measures of infant heart.

An increasing number of studies have found evidence for indirect pathways between prenatal exposure to cocaine and developmental outcomes in young infants. For example, one recent study found that the effects of prenatal cocaine exposure on development at birth, 1 month (Brazelton Neonatal Behavioral Assessment Scale) and 6 months of age (Bayley Scales of Infant Development) were mediated through the prenatal use of alcohol and tobacco and through the infant's head circumference (HC) at birth (Behnke, Eyler, Garvan, Wobie, & Hou, 2002). Specifically, cocaine exposure was associated with increased substance use and a smaller HC which were then associated with negative developmental outcomes. Thus, one goal of this study is to examine whether prenatal exposure to cocaine has a direct impact on infant regulation at 1 month of age or whether there is an indirect impact through other influences such as growth at birth or other maternal substance use during pregnancy. Furthermore, it is possible that cocaine has a dose-dependent effect on infant HR. In fact, a handful of studies have found evidence for cocaine-related effects on various aspects of infant development if samples were divided into heavy or moderate levels of exposure (S. W. Jacobson, Jacobson, Sokol, Martier, & Chiodo 1996; Lester et al., 2003). Thus, if existing studies on HR in cocaine-exposed infants included a large number of infants who were prenatally exposed to light amounts of cocaine, any effects associated with heavier maternal cocaine use can not be assessed. Consequently, a second goal of this study was to examine the possibility that there is a dose-dependent effect of cocaine on infant HR measures.

Evidence is accumulating that suggests that infant growth may mediate the association between prenatal exposure to cocaine and infant arousal. There are consistent findings of an association between maternal cocaine use during pregnancy and reduced infant growth at birth (Covington, Nordstrom-Klee, Ager, Sokol, & Delaney-Black, 2002; Eyler, Behnke, Conlon, Woods, & Wobie, 1998; Richardson, Hamel, Goldschmidt, & Day, 1999; Zuckerman, Frank, Hingson, & Amaro, 1989). Both norepinephrine and serotonin related effects of cocaine on vascular tone have been reported, resulting in decreased placental blood flow and fetal vasoconstriction (Institute of Medicine, 1996). This reduced blood flow has been implicated as a causal mechanism for the effects of prenatal cocaine exposure on poor fetal growth (Handler, Kistin, Davis, & Ferre, 1991; Oro & Dixon, 1987). Maternal cocaine use is also associated with poor maternal nutrition and lack of prenatal care, thus exacerbating the likelihood of poor fetal growth in this group of children (Amaro, Zuckerman, & Cabral, 1989). Furthermore, infant growth has been linked to arousal difficulties in infants that persist at least into the preschool years. In fact, low birth weight (BW) is the single best predictor of maternal ratings of behavioral regulation as measured by the Child Behavior Checklist and Parenting Stress Index scores at 3 years of age (Doussard-Roosevelt, Porges, Scanlon, Alemi, & Scanlon, 1997). Thus, these findings suggest that the association between prenatal exposure to cocaine and infant arousal may be indirect through infant growth.

Other caregiver and infant characteristics also may moderate and/or mediate the association between prenatal exposure to cocaine and infant arousal. Specifically, because maternal cocaine use is likely to be associated with the use of other substances, including alcohol, marijuana, and nicotine (Lester et al., 2003), other substance use by women during pregnancy may function as a mediator of this association. Alcohol and nicotine in particular are known to have significant teratological influences on regulatory processes (Gingras & O'Donnell, 1998). Thus, exposure to other substances, specifically alcohol and cigarettes, may also mediate the association between maternal cocaine use during pregnancy and infant

arousal. Recent studies have also suggested that the relation between prenatal exposure to cocaine and development outcomes may be moderated by infant growth and caregiver characteristics such as maternal age and relationship of the primary caregiver to the infant (Covington et al., 2002; Frank et al., 2002). Consequently, another goal of this study was to determine whether caregiver variables and/or infant growth moderate any existing association between prenatal exposure to cocaine and infant regulation.

The purpose of this study was to examine the association between prenatal exposure to cocaine and infant arousal at 4–8 weeks of age. We tested the possibility that the association between prenatal exposure to cocaine and infant arousal would be mediated by two risk variables: infant growth and other maternal substance use during pregnancy, using the procedure for mediational analysis outlined by MacKinnon and colleagues (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Furthermore, we tested the possibility that maternal age and infant growth would moderate the association between prenatal exposure to cocaine and infant arousal. Specifically, we hypothesized that infants who were prenatally exposed to cocaine and had older mothers or smaller fetal growth indicators would have higher HR and lower RSA.

Method

Participants

Participants consisted of 77 cocaine-exposed and 64 comparison mother–infant dyads recruited into an ongoing longitudinal study of maternal substance use and child development. An outreach worker on the project staff recruited all participants after delivery from two local area hospitals. Mothers ranged in age from 18 to 39 (M = 32.43, SD = 7.93). The majority of mothers were African American (61%), were receiving Aid to Families with Dependent Children (AFDC, 71%) at the time of their first laboratory visit (2001–2003), and were single (60%). The two groups were matched on maternal education, maternal age, maternal race/ethnicity, and infant gender. Forty-eight percent of the infants were male. As shown in Tables I and II, comparison infants had a significantly longer gestation, increased BW, birthlength (BL), and HC than cocaine-exposed infants. Eighty-four percent of the cocaine exposed and 96% of the comparison infants were full-term (≥37 weeks' gestational age). The study received approval from the institutional review boards of the hospitals as well as the primary institutions with which the authors are affiliated. In addition, informed written consent was obtained from all recruited participants and Health Insurance Portability and Accountability (HIPPA) of 1996 authorization was obtained from all participants recruited after April, 2003. Participants received $30.00 in the form of gift certificates and a $5.00 infant toy at the 4- to 8-week visit for their participation.

Assessment of Growth and Risk Status—Three measures of growth at birth were used in this study: BW (in grams), BL (in centimeters), and HC (in centimeters). 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 was also used to complete the Obstetrical Complication Scale (OCS; Littman & Parmelee, 1978), a scale designed to assess the number of perinatal risk factors experienced by the infant. Higher numbers on this scale indicate lower risk status.

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 and, thus, were available through chart review for 128 (91%) of the mothers in the study at the time of recruitment. Hair analysis was available for 103 (73%) of the mothers. Eleven percent of the sample refused to give a hair sample and the remaining mothers had hair that was too short for analysis. 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.

Urine toxicologies consisted of standard urine screening for drug level or metabolites of cocaine, opiates, benzodiazepines, and tetrahydrocannabinol (THC). Urine was rated positive if the quantity of drug or metabolite was >300 g/mL. Hair samples were collected from the mothers at the first laboratory visit and sent to Psychemedics Corporation for radioimmunoanalyses (RIAH). Hair samples were screened for cocaine, followed by a gas chromatography/mass spectrometry (GC/MS) confirmation of 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 half an inch per month, it can record a pattern of drug consumption related to the amount and frequency of use (Baumgartner, Black, Jones, & Blahd, 1982). Thus, a two-inch length of hair could contain a record of approximately 4 months of use, and given adequate hair length (about 4–5 in.), use per trimester may be recorded. Drugs become detectable in hair about 3–4 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 (Magura, Freeman, Siddiqi, & Lipton, 1992). GC/MS confirmations of RIAH have not revealed any false positives because of testing errors (Magura et al., 1992).

Approximately 29% (81% of the mothers in the cocaine group) of mothers in the study had positive urine toxicologies at delivery, and 30% of mothers (82% of the mothers in the cocaine group) had hair samples that tested positive for cocaine during pregnancy. The remainder of mothers in the cocaine group admitted having used cocaine in the brief, self-report screening instrument administered after delivery. Mothers in the comparison group reported not having used any illicit substances other than marijuana and had hair and urine samples that were negative for all illicit substances except marijuana. Additional exclusionary criteria for all mothers consisted of the following: maternal age of 18 or younger, use of illicit substances other than cocaine or marijuana, and significant medical problems for the infant (e.g., genetic disorders, major perinatal complications, baby in critical care for over 48 h).

Infant Physiological Assessment—At 4–8 weeks of age (4–8 weeks adjusted age for preterm infants), infants were tested in a quiet examining room. Examiners were blind to infant group status. Because behavioral state can impact HR, testing was conducted while infants were in a sleep state. A five-channel Bioamp (James Long Company) recorded respiration and electrocardiograph (ECG) data. Disposable electrodes were triangulated on the infant's chest. A respiration bellows was placed at the height of the zyphoid process to measure inspiration and expiration. The infant was then placed in a bassinet. Following a five-minute period of undisturbed acclimation to the equipment and bassinet, 10 min of undisturbed physiological data were recorded online directly into a data acquisition computer.

Interbeat interval (IBI) analysis software (James Long Company, 1999) was used to process the HR data and to calculate RSA. HR samples, which were collected every 10 min, were used to calculate mean HR per one-second period. A level detector was triggered at the peak of each R-wave. The interval between sequential R-waves was calculated to the nearest

millisecond. Data files of R-wave intervals were later manually edited to remove incorrect detection of the R-wave or movement artifacts. The software computes RSA by using respiration and IBI data as suggested by Grossman (1983). The difference between maximum IBI during expiration and the minimum IBI during inspiration was calculated. The difference, which is measured in seconds, is considered to be a measure of RSA, and is measured twice for each respiration cycle (once for each inspiration and once for each expiration). The time for inspirations and expirations is assigned as the midpoint for each. The time for each arrhythmia sample is assigned as the midpoint between an inspiration time and an expiration time. The software synchronizes with respiration and is, thus, relatively insensitive to arrhythmia due to tonic shifts in HR, thermoregulation, and baroreceptor. Average RSA and HR variables were calculated for the 10-minute period of sleep. Decreased RSA is thought to index a dysregulated affective style (Beauchaine, 2002).

Maternal Substance Use—The Timeline Follow-back Interview (TLFB) was used to assess maternal substance use before, during, and after pregnancy at the 1 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 and has good test–retest reliability and is highly correlated with other intensive self-report measures (Brandon, Copeland, & Saper, 1995; Brown, Burges et al., 1998). The TLFB yielded data about the number of days cocaine was used and the amount of money spent on cocaine for the month before and after pregnancy and for each trimester of pregnancy. The TLFB also yielded data about other substance use (alcohol, marijuana, cigarettes). The use of the TLFB for these substances resulted in the following variables for each of the substances used for the month before pregnancy, each trimester of pregnancy, and for the month following pregnancy: number of days used, total number of joints used (for marijuana), total number of cigarettes smoked, and total number of standard drinks, mean standard drinks per drinking day and number of days drinking 5 or more drinks (for alcohol).

Total number of days of cocaine use during pregnancy for users ranged from 1 to 252 days (M = 39.73, SD = 4.28). The amount of cocaine found in hair determined from sectional analysis ranged from 0 to 4226 ng/10 mg of hair during pregnancy (M = 178.04, SD = 8.82). There was a considerable amount of discrepancy between self-reported cocaine use and the hair analyses results. Out of the 55% of mothers who reported no cocaine used during the pregnancy, 14% tested positive for cocaine via hair analysis. Thus, both data obtained from the TLFB interview on cocaine use during pregnancy and from maternal hair analysis were used to identify women as light, heavy or noncocaine users. Consistent with other studies (S. W. Jacobson et al., 1996), heavy cocaine use was defined as use of cocaine 2 or more days per week during the first trimester of pregnancy or the top quartile of hair analysis results among the cocaine users (>304.2 ng/10 mg of hair). Mothers who used less cocaine during pregnancy were assigned to the light cocaine use group. See Table II for information about other substance use in these groups.

Results

Sample Characteristics

Descriptive statistics for the demographic and risk status variables for both mothers and infants of the three exposure groups are presented in Table I. Results of one-way Analyses of Variance (ANOVA) indicated that mothers who used light amounts of cocaine during pregnancy were significantly older than both nonusers and heavy users. In addition, women who did not use cocaine during pregnancy received more prenatal care, had a higher

socioeconomic status (SES), as measured using the Hollingshead (1975) scale, and higher parity than women who used either light or heavy amounts of cocaine during pregnancy. Nonusers also had significantly more years of education than heavy users. Finally, women who used heavy amounts of cocaine during pregnancy consumed more alcohol drinks and were more likely to drink heavily when they did drink than nonusers and women who used light amounts of cocaine during pregnancy (Table II). Although marijuana use during pregnancy was high in the comparison group, reflecting the normative use of marijuana in this high-risk sample, it is important to note that there was no significant difference between groups.

Fetal growth, risk status and HR measures also significantly differentiated the three exposure groups. As shown in Table II, infants who were prenatally exposed to heavy amounts of cocaine had significantly smaller BLs and HCs than nonexposed infants. In addition, infants of both light and heavy users weighed less at birth than nonexposed infants. Nonexposed infants also had significantly longer gestations (range = 38.93–39.68) than infants prenatally exposed to heavier amounts of cocaine (range = 37.27–39.1). As shown in Table I, cocaine-exposed infants had a higher level of perinatal risk reflecting a constellation of risk factors associated with maternal cocaine use including a history of maternal substance use, higher parity, and reduced fetal growth and gestational age.

Association Between Cocaine Use and Heart Rate Variables—Finally, infants prenatally exposed to both light heavy amounts of cocaine had significantly higher HR than the other two groups of infant and infants exposed to light amounts of cocaine had significantly higher HR than nonexposed infants. Given the small sample size for the heavy cocaine-exposed group, we calculated effect sizes (*r*) for the HR variables Examination of the effect size for control versus heavy cocaine use during pregnancy on HR indicated a large effect size ($r = -0.67$). ANOVA results also indicated a marginal group difference for RSA, $F(2,116) = 2.76$, $p = .06$. Examination of this effect size indicated a moderate to large effect size ($r = 0.30$) for control versus heavy cocaine use, suggesting that the failure to find a significant group difference for RSA is the result of low power due to a relatively small number of heavy cocaine users.

Mediational Analyses—The next step was to examine whether there was an indirect association between maternal cocaine use during pregnancy and physiological regulation via fetal growth. Two approaches to examining indirect or mediational pathways have been discussed in recent years (MacKinnon et al., 2002). The first is the widely used causal steps approach to mediation that clearly specify that in order to test mediation, the independent (IV), dependent (DV), and mediator variables must all be associated with each other (Baron & Kenny, 1986). The shortcomings of this method have recently been discussed in the literature. The causal steps approach has been faulted because it does not provide a statistical test of the indirect effect of an IV on a DV via a third variable; that large sample sizes (n = 500 or more) are required to have adequate power to test mediational effects with small to medium effect sizes; and that the condition that IV and DV have to be significantly associated with each other excludes many “inconsistent” intervening variable models in which the direct and indirect effects have opposite signs and may cancel each other out (MacKinnon, Krull, & Lockwood, 2000). Given the lack of a strong association between maternal cocaine use and RSA, we chose to analyze the role of fetal growth using an intervening variable approach discussed by MacKinnon et al. (2000, 2002).

Three intervening variables were considered and analyzed separately due to concerns about multicol-linearity, BW, BL, and HC at birth for each of the two dependent measures (HR and RSA). Cocaine group status was dummy coded (no cocaine vs. light or heavy use and no or light cocaine vs. heavy use). The first step in this process was to estimate the

association between maternal cocaine use and the individual growth measures by using Linear Regression with the fetal growth measure (BW, BL or HC) as the criterion variable and maternal cocaine use as the predictor (see Table III). These analyses indicated that maternal cocaine use was significantly associated with BW, BL and HC. In the next step, the association between the fetal growth measures and HR was estimated after controlling for gestational age. Hierarchical Linear Regression was used with HR as the criterion variable. To control for any possible effect of differences in age, gestational age was entered in the first step, followed by fetal growth (see Table III). The Product of Coefficients Test for the intervening variable effect was used to calculate the significance of the indirect effect (see MacKinnon et al., 2002). Standard error for this test was calculated using the formula derived by Sobel (1982). The significance of the intervening variable effect was tested by dividing the estimate of the intervening variable effect by its standard error, which was then compared to the values of the normal distribution (MacKinnon et al., 2002). The intervening variable effect for BW when comparing heavy cocaine using mothers to nonusing mothers was significant, $z = 2.46$, $p < .05$. Thus, mothers who used heavier amounts of cocaine during pregnancy had infants with lower BWs, and infants with lower BWs had higher HRs. None of the other fetal growth variables met criteria for an intervening variable effect with HR as the criterion variable.

The same procedure was followed to examine fetal growth measures as potential intervening variables of the association between maternal cocaine use and RSA at 4–8 weeks of age. None of the fetal growth variables mediated the association between maternal cocaine use and RSA.

Similarly, maternal cigarette smoking (total number of cigarettes smoked during pregnancy) and alcohol use (mean number of standard drinks per drinking day and number of days where 4 or more drinks containing alcohol were consumed) were examined as possible mediators of the association between cocaine exposure and infant HR and RSA. Maternal cocaine use during pregnancy was associated with total number of cigarettes smoked during pregnancy and with both measures of alcohol use during pregnancy (Table IV). Mothers who used more cocaine during pregnancy also smoked significantly more cigarettes, consumed a higher average number of standard drinks per day and had more incidences of binge-drinking. However, none of the substance use variables accounted for significant variance in HR (Table IV). Consequently, these variables were no longer considered as potential mediators of the association between HR and maternal cocaine use during pregnancy. The same procedure was conducted to examine maternal cigarette smoking and alcohol consumption during pregnancy as predictors of infant RSA. These results also indicated that none of the substance use variables were associated with RSA (Table III). Thus, maternal cigarette smoking and alcohol use during pregnancy as potential mediators of the association between prenatal exposure to cocaine and RSA were not examined further.

Moderational Analyses—Regression analysis was used to test whether the association between maternal cocaine use during pregnancy and infant regulation were moderated by maternal age or infant growth. Separate regression models were conducted for the two dependent measures (HR and RSA) and the four moderators (maternal age, BW, BL, and HC at birth). This resulted in a total of eight regression models. A two-step hierarchical regression approach was used. First, the dummy coded cocaine use variable and the moderator were entered into the regression equation. The interaction terms were entered into the regression equation in the second step. This term was the product of the dummy coded cocaine use variable with the *z*-transformed potential moderator (maternal age, or infant growth) as recommended by Baron and Kenny (1986). Evidence for the moderating effect of maternal age or infant growth could be established at this step if the interaction term

explained a significant proportion of the variance over and above that accounted for by the main effects of its two contributing variables (Baron & Kenny, 1986). None of the interaction terms were a significant predictor of HR and RSA indicating that neither maternal age nor infant growth moderated the association between prenatal exposure to cocaine and infant HR.

Discussion

The primary goal of this study was to examine the relation between prenatal exposure to cocaine and physiological regulation at 4–8 weeks of age and to assess potential mediators and moderators of this association. The results indicated that prenatal exposure to cocaine was significantly related to physiological measures of infant regulation. We also found that BW, but not BL, birth HC or other substance use mediated the relationship between cocaine exposure and resting HR.

The first finding was a dose-dependent effect of cocaine exposure on resting HR and RSA. Infants who had been exposed to the heaviest levels of cocaine had the highest HR followed by infants who had been exposed to lighter amounts of cocaine. This finding of an increased resting HR differs from those of previous studies that have found either a decreased HR in cocaine-exposed neonates (Silvestri et al., 1991) or no difference in resting HR between cocaine-exposed and nonexposed neonates (DiPietro et al., 1995; Mehta et al., 1993). Contrary to the findings of other studies (DiPietro et al., 1995; Mehta et al., 1993; Silvestri et al., 1991), we also found that infants who had been exposed to heavy amounts of cocaine during pregnancy had significantly lower RSA than nonexposed infants or infants exposed to lighter amounts of cocaine. These findings are particularly important because increased HRs and reduced HRV or RSA are findings that have been seen in other groups of high-risk infants with compromised nervous systems (DiPietro, Caughy, Cusson, & Fox, 1994; Porges, 1992).

One explanation for these conflicting findings is the difference in the age of the infants. Previous studies assessed HR in the first days of life rather than when the infants were 4–8 weeks of age. Consequently, it is possible that differences in physiological regulation may not be evident until after the transition to extrauterine life is completed.

A second explanation may be the difference in how mother–infant dyads were assigned to groups. Rather than dichotomizing cocaine use into exposed or non-exposed groups, examining multiple levels of cocaine exposure may be more effective in identifying possible dose-dependent effects of cocaine on regulation. In fact, our finding of the highest HR in the heavily exposed infants is consistent with other findings reported by several investigators that suggest that differential outcomes are associated with heavier exposure to cocaine (S. W. Jacobson et al., 1996; Lester et al., 2003). Thus, these findings highlight the importance of examining the possibility of dose-dependent effects when studying the development of infants prenatally exposed to cocaine.

The second interesting finding was the pattern of relations between cocaine exposure, BW and HR. The pathway linking heavy cocaine exposure to HR was mediated by BW. Specifically, exposed infants who experience the greatest reductions in BW show higher levels of arousal at 4–8 weeks of age. This provides empirical evidence supporting one specific mechanism by which cocaine exposure may impact physiological regulation during early infancy. The manner in which cocaine exposure impacts fetal growth is fairly well understood. This study indicates that this process continues to impact nervous system functioning beyond the neonatal period. Because considerable literature has reported that increased physiological arousal early in infancy predicts less optimal cognitive, social and

emotional development, the mediational influence of BW may explain, in part, disruptions in behavioral regulation that are seen later in infancy and into the school years.

Finally, it is important to note some of the limitations of this study. First, although care was taken in this study to identify substance use in this sample, the accurate assessment of substance use is difficult. Pregnant women are often hesitant to divulge information regarding the use of substances during pregnancy, particularly of illicit substances such as cocaine. To address this issue, multiple indices of substance use were used including self-report by using the reliable Timeline Followback Interview, as well as analysis of hair and urine samples. Each of these measures has its own limitations. However when used in combination, the likelihood of accurately identifying substance use is increased.

Second, the number of mother–infant dyads in the heavy exposure groups was fairly small increasing the chance that a few extreme data points may have influenced the findings. On the other hand, the finding of significant group differences despite this small group size suggests that these findings are very strong. However, future studies should explore this dose-dependent effect with a larger sample of mothers who used heavier amounts of cocaine during pregnancy.

Finally, it is unclear from this study whether the effects of cocaine on infant regulation will persist beyond the first months of life. Although other studies have found evidence that regulatory difficulties are present in older cocaine-exposed infants (Bendersky & Lewis, 1998a,b; Mayes, L. C., Bornstein, M. H., Chawarska, K., & Granger et al., 1995, 1996), the methods used to assess regulation were different. Furthermore, HR and RSA continue to develop during infancy. Resting HR gradually decreases across the first year of life and RSA steadily increases during infancy due to various factors such as myelinization of vagal fibers (Bornstein & Suess, 2000). Thus, even though this study statistically controlled for gestational age, it is possible that the group differences in HR and RSA seen at 4–8 weeks of age may be the results of physiological immaturity related to a reduced gestation. Consequently, it is unclear whether the findings of differential regulation in older infants would be found with the physiological measures used in this study.

Despite these limitations, these findings are important because they provide additional support for the influence of prenatal exposure to cocaine on infant regulation and indicate that one pathway from cocaine exposure to altered regulation may be through BW. Furthermore, the combination of an increased HR and marginally lower RSA in infants exposed to heavy amounts of cocaine is a pattern suggestive of a compromised nervous system at 4–8 weeks of age. Finally, these findings highlight the importance of considering level of exposure rather than just treating cocaine use during pregnancy as a dichotomous variable.

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Table I

Maternal and Infant Characteristics and Cocaine Use

	Abstainers (*n* = 64)		Light users (*n* = 55)		Heavy users (*n* = 22)		
	M	***SD***	***M***	***SD***	***M***	***SD***	***F***
Maternal characteristics							
Age (years)	29.3[a]	5.05	32.42[a]	5.25	31.41	5.59	4.66**
Education (years completed)	12.34[a]	1.78	11.89	1.89	11.0	2.05	4.29*
S.E.S. (Hollingshead two-factor)	3.66[a]	1.84	2.84[a]	1.4	2.05[a]	.95	9.86**
Parity	3.44[a]	1.71	4.32[a]	2.01	3.77	2.14	3.16*
Prenatal care (number of visits)	14.41	7.7	14.22	7.89	10.53	7.55	1.95
Number of days cocaine used during pregnancy	0[a]	0	19.28[a]	25.98	89.93[a]	84.07	49.41**
Hair analysis—level of cocaine in last 90 days	0[a]	0	63.38[a]	85.69	752.07[a]	1097.22	18.16**
Infant characteristics							
Age at 4– to 8-week visit (weeks)	5.59	1.34	5.80	2.08	5.76	1.62	.78
Gestational age (weeks)	39.30[a]	1.37	38.48[a]	1.8	38.18[a]	2.06	4.73**
Weight at 1 month of age (grams)	5052.92	2598.75	4290.18	851.47	5352.36	1077.56	2.21
Length at 1 month of age (centimeters)	53.95[a]	3.72	52.19[a]	4.53	52.14[a]	3.47	3.41*
Head circumference at 1 month of age (centimeters)	37.44	1.81	36.99	1.78	36.57	1.84	2.16
Apgar 1	8.33	1.41	8.3	1.30	8.55	0.67	0.29
Apgar 5	8.87	0.48	8.88	0.63	9.00	0	0.56
Obstetrical complications scale (OCS)	91.42[a]	11.81	82.60[a]	12.85	81.91[a]	15.76	7.40**
Gender (% male)	45		51		46		

[a]Where the significant differences lie.

*$p < 0.05$.

**$p < 0.01$.

Table II

Group Differences for Outcome and Mediator Variables

	Abstainers		Light users		Heavy users		
	M	***SD***	***M***	***SD***	***M***	***SD***	***F***
Mediator variables							
Birth weight (grams)	3353.85[a]	548.6	2903.27[a]	556.35	2811.09[a]	486.03	12.37**
Birthlength (centimeters)	49.62[a]	3.31	48.57[a]	2.45	46.98[a]	2.61	6.54**
Birth head circumference (centimeters)	33.66[a]	1.45	33.01	1.48	32.84[a]	1.47	3.64*
Total number of cigarettes smoked during pregnancy	522.39[a]	1013.45	1571.5[a]	1549.54	2361.32[a]	2077.19	16.13**
Total number of standard drinks	10.54[a]	39.27	95.1[a]	234.7	524.05[a]	871.63	5.92**
Number of days 5 or more drinks were consumed	1.06[a]	3.99	4.29[a]	11.91	52.32[a]	89.65	17.74**
Total number of joints during pregnancy	71.85	349.61	57.14	129.46	37.05	77.4	.17
Outcome variables							
Heart rate (bpm)	134.06[a]	139.20	143.1[a]	150.21	148.86[a]	158.53	21.43*
Respiratory sinus arrhythmia	.019	.038	.019	.031	.010	.017	2.76, $p = .06$

[a] Where the significant differences lie.

* $p < 0.05$.

** $p < 0.01$.

Table III

Hierarchical Linear Regression Models—Mediational Analyses for Heart Rate

	Unstandardized coefficients		Standardized		
Predictor variables	**β**	***SE***	**β**	R^2	***F***
Regression 1: outcome—BW					
Gestational age	187.73	23.36	.554**	.46	34.86**
Abstainers vs. users	−317.78	88.16	−.267**	—	—
Abstainers/light vs. heavy users	−30.45	112.19	−.02	—	—
Regression 2: outcome—BL					
Gestational age	.79	.149	.429**	.27	14.74*
Abstainers vs. users	−.594	.530	−.098	—	—
Abstainers/light vs. heavy users	−1.301	.686	−.163	—	—
Regression 3: outcome—HC					
Gestational age	.351	.077	.385**	.21	—
Abstainers vs. users	−.498	.273	−.166	—	10.22**
Abstainers/light vs. heavy users	−.019	.354	−.005	—	—
Regression 4: outcome—HR					
Birth weight	−.006	.002	−.288**	.083	9.56*
Regression 5: outcome—HR					
Birthlength	−1.35	.46	−.28**	.078	8.66*
Regression 6: outcome—HR					
Head circumference	−2.36	.85	−.265**	.07	7.71*

BW, birth weight; BL, birthlength; HC, head circumference; HR heart rate.

* $p < 0.05$.

** $p < 0.01$.

Table IV

Correlation Matrix for Variables in the Models

	Cocaine use	Cigarette use	Number of standard drinks/ pregnancy	Number of days 5 or more drinks consumed	Maternal age	Birth weight	Birthlength	Head circumference	Heart rate
Cocaine use	—	—	—	—	—	—	—	—	—
Cigarette use	.50*	—	—	—	—	—	—	—	—
Number of standard drinks/ pregnancy	.70**	.32**	—	—	—	—	—	—	—
Number of days 5 or more drinks consumed	.72**	.37**	.94**	—	—	—	—	—	—
Maternal age	.07	.09	.04	.03	—	—	—	—	—
Birth weight	−.14**	−.32**	−.02	−.02	−.16	—	—	—	—
Birthlength	−.18*	−.20	.01	.00	−.15	.66**	—	—	—
Head circumference	−.13	−.27**	−.01	−.03	−.08	.68**	.47**	—	—
Heart rate	.35*	.11	−.11	−.11	−.06	−.30**	−.28*	−.39**	—
Respiratory sinus arrhythmia	−.09	.19	−.17	−.16	−.06	.24*	.21*	.14	−.25**

* $p < .05$.

** $p < .01$.