Published in final edited form as:

Dev Psychobiol. 2007 April ; 49(3): 276–289. doi:10.1002/dev.20215.

Prenatal Cocaine and Other Substance Exposure: Effects on Infant Autonomic Regulation at 7 Months of Age

Pamela Schuetze,

Department of Psychology, State University of New York College at Buffalo State College, Buffalo, NY; Department of Pediatrics and Research Institute on Addictions, University at Buffalo, Buffalo, NY

Rina D. Eiden, and

Department of Pediatrics and Research Institute on Addictions, University at Buffalo, Buffalo, NY

Claire D. Coles

Emory University School of Medicine, Atlanta, GA

Pamela Schuetze: schuetp@buffalostate.edu

Abstract

This study examined the association between prenatal exposure to cocaine and autonomic regulation at 7 months of age. Heart rate (HR) and respiratory sinus arrhythmia (RSA) were obtained from 154 (79 exposed, and 75 nonexposed) infants during baseline and tasks designed to elicit positive and negative affect. Cocaine-exposed infants had higher HR during the positive affect task. There was a significant suppression of RSA during the negative affect task for nonexposed infants but not for exposed infants. Fetal growth and maternal caregiving behavior did not mediate or moderate this association. These results provide additional support for an association between prenatal cocaine exposure and dysregulation during infancy.

Keywords

autonomic regulation; prenatal cocaine exposure; respiratory sinus arrhythmia; maternal negative affect

Introduction

Prenatal exposure to cocaine has been associated with altered postnatal behavior particularly in the realm of arousal and behavioral organization. Cocaine has been shown to inhibit the reuptake 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 (Gawin & Ellinwood, 1988; Nassogne, Evrard, & Courtoy, 1998). The regions of the brain that are rich in monoamines are the centers involved in regulatory activities and reactivity to stress (Robbins, 1997; Tucker & Williamson, 1984). In fact, a growing body of evidence suggests that prenatal exposure to cocaine may have a significant impact on the development of regulatory processes in infants. These regulatory difficulties include poorer state regulation, more difficulty being calmed, increased physiological arousal, and differential physiological responding to sensory challenges, as measured by heart rate, heart rate variability, and cortisol levels, beginning in the neonatal

period and persisting throughout the first year of life (Bard, Coles, Platzman, & Lynch, 2000; Bendersky & Lewis, 1998a,b; Brown, Bakeman, Coles, Sexson, & Demi, 1998a; DiPietro, Suess, Wheeler, Smouse, & Newlin, 1995; Gingras, Weese-Mayer, Hume, & O'Donnell, 1992; 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; Schuetze & Eiden, 2006).

Reactivity and Regulation in Infancy

These findings are particularly significant when considering that one of the primary developmental tasks for infants is to cope with sensory challenges from the external environment as well as to adequately perform homeostatic processes in the presence of both endogenous and exogenous sources of stimulation (DeGangi, DiPietro, Greenspan, & Porges, 1991). During the first weeks of life, the immaturity of sensory systems buffers infants from external stimulation (Sroufe, 1979). Consequently, regulation tends to be endogenously based (Gable & Isabella, 1992). Beyond the neonatal period, the regulatory system consists of the ability of the infant to regulate the latency and intensity of reactions to environmental stimulation (reactivity) as well as use strategies that would modulate these reactions (regulation). Thus, an emerging developmental task for infants beyond early infancy is learning to modulate positive and negative emotional experiences (e.g., Kopp, 1989; Ungerer, Dolby, Waters, Barnett, Kelk, & Lewin, 1990).

Autonomic Indices of Reactivity and Regulation

Measures of heart rate may be particularly useful indices of reactivity and regulation during infancy. The regulation of heart rate is believed to reflect both autonomic function and neurological integrity. The influence of the central nervous system on heart rate is mediated by both the sympathetic and parasympathetic nervous systems such that the role of the parasympathetic branch of the autonomic nervous system is to maintain homeostasis by regulating sympathetic excitation. Thus, increases in heart rate indicate increased autonomic arousal as a consequence of sympathetic system activity or parasympathetic withdrawal (e.g., Richards, 2001). An increase in HR in response to affect arousing stimuli is indicative of physiological arousal or reactivity, which impacts both the quality and quantity of infant responsiveness to stimulation. A moderate increase in HR in response to environmental challenge may be indicative of a normative autonomic response. However, high levels of reactivity as indicated by a more extreme change in HR may not reflect an optimal response.

One index of parasympathetic regulation that has been widely discussed in the developmental literature is respiratory sinus arrhythmia (RSA; Beauchaine, 2001; Porges, 1991). RSA can be measured by isolating the variability in heart rate due to respiration. The difference in the R-R interval between inspiration and expiration is believed to reflect the cardiac vagal tone outflow and is widely used as an index of cardiac vagal tone (Camm et al., 1996; Eckberg, 1983; Katona & Jih, 1975). In fact, one important role of RSA is to regulate cardiac output in the face of environmental challenge. Specifically, the ability to suppress RSA (applying the vagal brake) during exposure to external stimulation is indicative of optimal parasympathetic regulation. Optimally, the sympathetic and parasympathetic systems should act in concert such that when sympathetic arousal (measured by HR in this study) increases in response to environmental challenge, there should be a decrease in parasympathetic activity (measured by RSA). This negative change in RSA from baseline to environmental challenge is associated with more optimal state regulation in infancy (DeGangi et al., 1991), decreased behavior problems in preschool-aged children (Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996), and more adaptive behavior during attention and affect eliciting tasks in both preschool and school-aged children (Calkins, 1997; Suess, Porges, & Plude, 1994), and during social approach (Stifter

& Corey, 2001). Thus, the measurement of change in RSA from baseline to challenging situations is an important concurrent and predictive index of parasympathetic regulation in infants.

Prenatal Cocaine Exposure and Autonomic Regulation

The majority of studies examining autonomic functioning among cocaine exposed infants have focused on resting heart rate and RSA in the neonatal period, and have yielded mixed results. For instance, studies have reported lower heart rates (Silvestri, Long, Weese-Mayer, & Barkov, 1991), greater high-frequency power as a portion of total spectral power (Mehta et al., 1993), and greater overall heart rate variability (Regalado et al., 1996; Regalado, Schechtman, Khoo, & Bean, 2001) in cocaine-exposed compared to noncocaine-exposed neonates. These studies suggest higher parasympathetic activity during rest among cocaine-exposed neonates. Conversely, other studies have not found any effects of maternal cocaine use on baseline HR or RSA during sleep (DiPietro et al., 1995; Mehta et al., 1993), perhaps due to lower sample sizes or lack of examination of dose–response effects. Baseline indices of HR and RSA are not as indicative of an infants' ability to modulate arousal beyond the neonatal period (DiPietro, Porges, & Uhly, 1992). However, few studies have examined changes in autonomic regulation in response to environmental challenge among cocaine-exposed infants. One exception is a study by Bard et al. (2000), who reported that prenatal cocaine exposure accounted for significant unique variance in arousal as measured by heart rate responses to stress among 8-week old infants.

Examining changes in autonomic functioning in response to affect arousing stimuli may be especially critical around the period when there are major biobehavioral shifts in emotional development. One such shift occurs around 7 months of infant age (Emde & Gaensbauer, 1981; Schore, 1994). Thus, the first goal of this study was to examine the association between prenatal cocaine exposure and infant autonomic regulation in response to affect arousing stimuli. We hypothesized that infants who had been prenatally exposed to cocaine would have higher HR in response to affect arousing procedures, reflecting higher reactivity or sympathetic arousal. We also hypothesized that cocaine-exposed infants would have a significantly smaller suppression in RSA following an environmental challenge, indicating poorer parasympathetic regulation.

Indirect Effects and Moderation

Theoretical frameworks such as the developmental psychopathology approach, as well as empirical evidence from studies using high-risk paradigms, suggest that there may be multiple pathways to risk. One such pathway for cocaine-exposed infants may be via compromised fetal growth. Reduced blood flow and fetal vasoconstriction have been implicated as causal mechanisms 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, lack of prenatal care, and lower pre-pregnancy weight, thus exacerbating the likelihood of poor fetal growth in this group of children (Amaro, Zuckerman, & Cabral, 1989). Fetal growth measures such as birthweight and gestational age, especially in the context of poor postnatal environment, have been linked a number of negative consequences including altered autonomic activity (e.g., DiPietro, Porges, & Uhly, 1992; Krafchuk et al., 1983; Lester et al., 1990). Thus, one pathway explaining potential associations between cocaine exposure and infant reactivity and regulation may be via compromised fetal growth. Fetal growth may also moderate this association (Brown et al., 1998a). In other words, fetal growth may interact with exposure status such that cocaine-exposed infants with poor fetal growth such as lower birthweight (controlling for gestational age) may be at highest risk for poor autonomic regulation.

Another pathway to poor autonomic regulation among cocaine-exposed infants may be through problematic maternal behavior. For instance, cocaine using mothers have been reported to display higher negative affect during interactions with their infants (Burns, Chetnik, Burns, & Clark, 1991a; Eiden, 2001; LaGasse et al., 2003), and be more disengaged and passive during mother–infant interactions (Gottwald & Thurman, 1994; Molitor, Mayes, & Ward, 2003). Maternal parenting behavior plays a critical role in helping children manage their arousal and keep distress within tolerable limits in infancy. A key aspect of this process is the affective quality of parent–child interactions in the first year of life (Feldman, Greenbaum, & Yirmiya, 1999; Schore, 1994; Tronick, 1989). Thus, a second pathway explaining the association between maternal cocaine use and infant regulation may be maternal affect during mother–infant interactions. Moreover, maternal affective behavior may also interact with exposure status to predict infant regulation. If infant affective arousal in response to environmental challenge is met with maternal negative affect, this is likely to result in greater infant affective and physiological dysregulation (Feldman et al., 1999; Schore, 1994; Calkins & Fox, 1992).

Consequently, a goal of this study was to examine if fetal growth and maternal affect mediated or moderated the association between prenatal exposure to cocaine and infant regulation. We hypothesized that both fetal growth and maternal negative affect may account for group differences in HR and RSA patterns in response to affect arousing procedures. We also hypothesized that fetal growth and maternal negative affect may moderate the association between cocaine exposure and infant regulation, such that the association between cocaine exposure and infant regulation would be stronger under conditions of poor fetal growth or higher maternal negative affect.

Finally, it is important to note that cocaine is a polydrug issue. The majority of women using cocaine also use alcohol, cigarettes, and marijuana. Alcohol and cigarettes have been known to have similar effects on infant regulation. Thus, the association between cocaine exposure and infant regulation can only be examined in the context of associations with other substance use.

Method

Participants

Participants consisted of mother–infant dyads recruited postpartum from two local area hospitals into a longitudinal study of maternal substance use and child development. Of the 170 mother–infant dyads that completed both laboratory visits, heart rate data from eight infants were lost due to technical problems. Thus, a total of 162 (80 nonexposed and 82 exposed) had heart rate data at 7 months of age. Of these 162 infants, 8 infants did not complete the physiological assessment due to extreme fussiness. These infants were not significantly different from infants who completed the physiological assessment in age, growth (fetal or postnatal), or prenatal substance exposure. Thus, the final sample consisted of 154 mother–infant dyads (75 nonexposed and 79 exposed).

Mothers ranged in age from 18 to 42 ($M = 29.97$, $SD = 5.74$). The majority were African-American (61%), single (60%), and were receiving Aid to Families with Dependent Children (AFDC, 71%) at the time of their first laboratory visit (Years 2001–2004). Women were classified as either cocaine-using or “abstainers” and the two groups were matched on maternal education, age, race/ethnicity and on infant gender. Forty-eight percent of the infants were male. Eighty-four percent of the cocaine-exposed and 96% of the comparison infants were full-term (>37 weeks gestational age). Additional exclusionary criteria for all participants consisted of the following: maternal age less than 18 years, use of illicit

substances other than cocaine or marijuana, and significant medical problems in the infant (e.g., genetic disorders, major perinatal complications, baby in critical care for over 48 h).

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 \$35.00 in monetary incentives at the 4–8 week visit and \$50.00 in the form of gift certificates, checks, and infant toys at the 7-month visit for their participation.

Procedure

At recruitment, mothers on postpartum units were approached by project staff at two local hospitals and were invited to participate in a study of maternal health and infant development. Interested and eligible mothers and caregivers were given detailed information about the study and asked to sign consent forms. Once a family was recruited into the cocaine group, a matching noncocaine group family was recruited, based on maternal age, race, education, and child gender. Of the 4,800 women screened at delivery, 340 were eligible for participation in either group. Of these, 35% either declined participation or were not enrolled in the study because they expressed initial interest but withdrew before formal enrollment. Mothers who participated were younger (more often, 18 to 25 years of age) compared to those who were eligible but not enrolled in the study, $\chi^2(2) = 19.15, p < .001$, and were less educated (more often, high school or below), $\chi^2(2) = 45.79, p < .001$. Mothers who participated were also more likely to be in the cocaine group (90% of the mothers eligible to be in the cocaine group participated) compared to those who were eligible but not enrolled, $\chi^2(1) = 50.26, p < .001$. The majority of the mothers in the cocaine group who were not enrolled in the study had children placed in nonmaternal care. There were no other differences on any of the other demographic variables between those who participated and those who were eligible but not enrolled.

About 2 weeks after delivery, caregivers were contacted and scheduled for the first laboratory visit, which took place when the infant was 4 to 8 weeks old. This visit included a caregiver interview, a feeding session, and infant and maternal physiological assessments. A second laboratory visit was scheduled when the infant was about 7 months old. This visit included a caregiver interview, feeding and play sessions that were videotaped, and behavioral and physiological assessments of infant reactivity and regulation. All of the 7-month assessments were conducted with the primary caregiver of the child at that time. For the current analysis, the data from the caregiver interviews at both time points and the physiological assessment of infants at the second time point were used.

Identification of Substance Use

Cocaine status was determined by a combination of maternal self-report, chart review which provided information about results of the urine toxicology, and maternal hair analysis. Self-report was obtained using the Timeline Follow-back Interview (TLFB; Sobell, Sobell, Klajner, Pavan, & Basian, 1986), which assessed 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, has good test–retest reliability and is highly correlated with other intensive self-report measures (Brandon, Copeland, & Saper, 1995; Brown et al., 1998b). The TLFB yielded data about the average number of days per week cocaine was used, the average number of joints of marijuana and the average number of cigarettes (tobacco) smoked per week, and the average number of standard drinks consumed

per week, as well as the mean standard drinks per drinking day and number of alcohol binges (five or more standard drinks) during pregnancy and for the postnatal period.

Urine toxicologies consisted of standard urine screening for drug level or metabolites of cocaine, opiates, benzodiazepines, and tetrahydrocannabinol (THC). Participating hospitals routinely conducted urine toxicologies at the first prenatal visit 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. 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 postnatal laboratory visit and sent to Psychomedics Corporation for radioimmunoanalyses (RIAH). Drugs and their metabolites are absorbed into the hair and can be extracted and measured providing a record of use over trimesters (depending on hair length). (see Baumgartner, Hill, & Blahd, 1989). Drugs become detectable in hair about 3 to 4 days after use, a time when cocaine is rendered undetectable by urinalysis and, thus, provide a reliable method for determining chronic use. Gas chromatography/mass spectrometry (GC/MS) confirmations of RIAH have not revealed any false positives because of testing errors (see Magura et al., 1992).

Forty-four percent of the mothers in the cocaine group had positive urine toxicologies at delivery, 67% of the mothers in the cocaine group had hair samples that tested positive for cocaine during pregnancy, 85% had positive history of cocaine according to medical chart review or acknowledged using cocaine in the brief, self-report screening instrument administered after delivery. Mothers were included in the cocaine group if they reported use, 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. Ten percent of mothers in the cocaine group were identified as cocaine users during pregnancy by medical record (that included urine toxicology information) alone or from the brief screening interview alone. Approximately .01% were identified on the basis of the TLFB alone and 16% were identified by hair analysis alone. Thus, the majority of mothers met more than one criteria for inclusion into the cocaine use group.

Mothers in the comparison group reported not having used any illicit substances other than marijuana and did not test positive for the drug. See Table 1 for information about other substance use in these groups.

Assessment of Fetal Growth and Risk Status

Three measures of growth at birth were used: birth weight (g), birth length (cm) and head circumference (in cm) taken by obstetrical nurses in the delivery room and recorded in the infant's medical chart. Following recruitment, research staff recorded this information from the charts as well as the information used to complete the Obstetrical Complication Scale (OCS; Littman & Parmalee, 1978), a measure of perinatal risk factors experienced by the infant. Higher numbers on this scale indicate a more optimal obstetric history.

Assessment of Infant Reactivity and Regulation

The physiological assessment of reactivity and regulation was recorded during a 3-min baseline period, a 2-min puppet show, and the two arm restraint trials (2 min) by examiners blind to infant group status. Infants were tested while seated in a high-chair. A five-channel Bioamp (James Long Company, Caroga Lake, NY) 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.

Recording of the physiological data began once the infant was observed to be in a stable, quiet, alert state. A resting state was induced by having the infant watch a 3-min segment of a neutral videotape “Baby Einstein”; (see Calkins, 1997 for similar procedures for inducing rest). Although this condition was not a true baseline because infant attention was engaged, it served to keep the infant seated quietly without eliciting affect, thereby minimizing movement artifact. All physiological data were recorded continuously online directly into a data acquisition computer.

Two different paradigms designed to elicit positive affect and anger/frustration were used. The positive affect paradigm consisted of a puppet game that measures positive affect in response to social stimulation using puppets for a standardized presentation. A scripted dialog was used which took approximately 90 s to present followed by 30 s during which the child was allowed to play with the puppets. The anger/frustration paradigm consisted of a gentle arm restraint episode, which is a widely-used, well-validated measure of anger/frustration used to assess infant regulation and reactivity (Goldsmith & Rothbart, 1996; Stifter & Braungart, 1995). In this episode, the child was allowed to play with an attractive toy for 30 s, until the child was engaged with the toy (first negative affect trial). The caregiver was asked to stand behind the child, place her hands on the child's forearms, move them to the child's sides, and hold them there for 30 s, while maintaining a neutral expression. After the first trial, the caregiver was again asked to play with the child for 30 s followed by a second trial (negative affect trial 2). The session was stopped at the caregiver's request or if the child reached a maximum distress code, defined as the child reaching the highest intensity of negative affect of a full cry. This occurred for 16 infants (7 nonexposed and 9 exposed) who were not included in subsequent data analyses. The child was allowed to play with the toy at the end of the two trials.

IBI Analysis software (James Long Company, 1999) was used to process the heart rate data and to calculate RSA. Heart rate samples, which were collected every 10 ms, were used to calculate mean HR per 1-s period (Buss & Goldsmith, 1998; Goldsmith & Rothbart, 1996). A level detector was triggered at the peak of each R-wave. The interval between sequential R-waves was calculated to the nearest millisecond (Buss & Goldsmith, 1998). 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 using respiration and interbeat interval (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 heart rate, thermoregulation, and baroreceptor. Unlike some methods of calculating RSA including Porges's moving polynomial algorithm (Porges, 1986), this method corrects for RSA using tidal volume which has been found to influence RSA independent of vagal tone (Grossman, Karemaker, & Wieling, 1991). However, despite the differences in calculating RSA, studies suggest that the various estimates of RSA are highly correlated with each other (Beauchaine, 2001).

Average RSA and HR variables were calculated for the 3-min baseline period, for the puppet show, and for each arm restraint trial. Because there were no significant differences in HR or RSA between the two negative affect (NA) trials, we created mean HR and RSA for the two trials. These composite variables were used in all subsequent analyses.

Maternal Behavior

Maternal behavior was assessed during a Free Play paradigm at the 7-month assessment. Parents were asked to interact with their infants as they normally would at home for 5 min in a room filled with toys. These free-play interactions were videotaped for later coding. The free-play interactions were coded using a collection of global 5-point rating scales developed by Clark, Musick, Scott, & Klehr (1980), 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 (Clark et al., 1980; Clark, 1999).

We used 21 items from the original scale that have been validated in previous studies to code maternal behavior. Exploratory factor analyses conducted with these 21 items yielded three scales for parenting behavior: positive engagement, sensitivity and negative affect. Positive engagement (PE) had an initial eigenvalue of 12.4 and explained 35% of the variance, maternal sensitivity (MS) had an initial eigenvalue of 3.9 and explained 26% of the variance, and maternal negative affect (MNA) had an initial eigenvalue of 2 and explained 18% of the variance. Based on these factor analyses, three composite parenting scales were created by taking the average of the individual items to create each composite. The PE scale consisted of items such as warm, kind tone of voice, expressed positive affect, enthusiastic, cheerful mood, amount and quality of verbalizations, and connectedness. The MS scale consisted of items such as amount and quality of physical contact, contingent responsiveness, structuring the environment, reading child cues appropriately, flexibility, and low intrusiveness. The MNA scale consisted of items such as angry, hostile tone of voice, expressed negative affect, angry hostile mood, and displeasure, disapproval, and criticism. The internal consistencies for these composite scales were quite high ranging from .93 for sensitivity to .95 for positive engagement and negative affect.

Two female coders rated parental behavior. Both coders were trained on the Clark scales by the second author and were unaware of group membership and of all other data. The inter-rater reliability was high, ranging from Intraclass correlations of .93 for negative affect to .97 for positive engagement and sensitivity.

Results

Descriptive Statistics

Multivariate analyses of variance (MANOVA) were conducted to examine group differences for the demographic, maternal substance use, infant risk status and growth variables for the two exposure groups (see Tab. 1). Results from MANOVA with the demographic variables as the dependent measures and group status (control, exposed) as the independent variable yielded a significant multivariate effect of group status, $F(5, 139) = 6.31, p < .001, \eta_p^2 = .18$. See Table 1 for results from univariate analyses followed by simple contrasts. Results from MANOVA with the substance use variables as the dependent measures and group status as the independent variable yielded a significant multivariate effect of group status, $F(5, 139) = 7.8, p < .001, \eta_p^2 = .18$ (see Tab. 1 for results from univariate analyses). Finally, results from MANOVA with the infant risk status variables as the dependent measures and group status as the independent variable yielded a significant multivariate effect of group status, $F(5, 139) = 5.63, p < .001, \eta_p^2 = .16$ (see Tab. 1).

Relations between Substance Exposure, Infant Growth, and Heart Rate Measures

We then examined the association between the prenatal and postnatal substance use, infant risk characteristics, maternal behavior, and heart rate variables (see Tab. 2 for correlations between mediators and dependent variables). Higher prenatal cocaine and cigarette exposure

was either significantly or marginally associated with higher HR during most of the conditions (r s ranging from .15 to .23, all p s < .10). Higher prenatal exposure to cocaine was associated with higher RSA during the affect eliciting conditions (r s ranging from .15 to .25, all p s < .10). Finally, increased head circumference at birth was associated with higher HR during both affect eliciting tasks (r s = .18 and .21, both p s < .10) and lower RSA at baseline. Finally, maternal negative affect and maternal sensitivity were both associated with HR and positive engagement was associated with birth-weight.

Group and Gender Differences for RSA and HR

Preliminary analyses examined whether there were gender differences for any of the HR or RSA measures. No such differences were found. Because of the possibility that there might be group differences in outcome measures between exposed infants in foster care and exposed infants still in the custody of their biological mother (e.g., Brown et al., 2004), we conducted analyses to see if there were differences in HR or RSA for infants whose primary caregiver was the biological mother ($n = 143$) as compared to infants who were in the care of someone other than the biological mother ($n = 11$). There were no group differences for HR or RSA measures.

Separate repeated measures analyses of covariance (ANCOVA) with Condition (baseline, PA, and NA) as the within subject factor, and group status (exposure, control) as the between subjects factor were conducted for RSA and HR. Variables that were correlated ($p < .10$) with either cocaine exposure or outcome (HR and RSA) variables were used as covariates (Figs. 1 and 2). Thus, covariates included were maternal alcohol and cigarette use during pregnancy, maternal age, maternal education, parity, measures of fetal growth (BW, BL, and HC) and gestational age. See Table 3 for means and standard deviations for HR and RSA variables. The ANCOVAs for HR, $F(10, 204) = 2.41, p < .05, \eta_p^2 = .097$, and RSA, $F(10, 204) = 2.36, p < .05, \eta_p^2 = .096$, both indicated a significant interaction effect of group by condition. Infants who were prenatally exposed to cocaine had a marginally higher HR and significantly lower RSA during baseline and had a significantly higher HR during the PA task than nonexposed infants. There were no group differences for RSA during the PA task or for HR or RSA during either trial of the NA task.

Group Differences in RSA Suppression in Response to Environmental Challenge

To assess physiological regulation during the affect eliciting procedures, change scores for the RSA and HR measures between paradigms were calculated (see Tab. 3). In order to assess physiological regulation to negative affect, we calculated mean HR and RSA for both the NA task. Thus, we calculated a change score for both RSA and HR from baseline to the PA task, and from baseline to the NA task. Negative scores indicate a decrease in HR and RSA.

Because physiological responses may be influenced by the Law of Initial Value (Lacey, 1956; Wilder, 1956), the association between the initial physiological values (i.e., baseline) and subsequent physiological responses was examined. Baseline HR was significantly associated with HR during all of the other conditions (r s ranging from .70 to .93, all p s < .05). Similarly, baseline RSA was significantly associated with RSA during all of the other conditions (r s ranging from .40 to .77, all p s < .05). Thus, consistent with the Law of Initial Value, measures of HR and RSA were adjusted for baseline levels. In order to obtain physiological responses scores that were statistically independent from the baseline levels, residualized change scores were created by regressing the change scores on the baseline values. These residualized change scores are used in all subsequent analyses.

Analyses of covariance (ANCOVA) were conducted to look at group differences in these change scores. As described above, maternal alcohol and cigarette use during pregnancy, maternal age, measures of fetal growth, and gestational age were included as covariates. Results showed that infants who were prenatally exposed to cocaine during pregnancy had a slight increase in RSA during the PA task while infants who were not exposed to cocaine had a slight decrease in RSA during the PA. This difference was marginal, $F(1,143) = 3.02$, $p < .09$, $\eta^2_p = .03$. In addition, infants who were prenatally exposed to cocaine had a significantly smaller decrease in RSA during the NA task than nonexposed infants, $F(1,143) = 4.25$, $p < .05$, $\eta^2_p = .07$. There were no significant group differences for HR change scores. Because prematurity may substantially impact physiological outcomes, in addition to statistically correcting for gestational age as described above, we also conducted these ANCOVAs without infants born prior to 37 weeks gestational age. There were no substantial differences in outcomes. Thus the group differences in HR and RSA in this sample was not influenced by prematurity.

Mediational Analyses

The next step was to examine if there was an indirect association between prenatal exposure to cocaine and autonomic regulation via fetal growth or maternal caregiving behavior. First, measures of fetal growth (birthweight, birthlength, and head circumference at birth) after controlling for gestational age were examined as possible mediators of the association between prenatal exposure to cocaine and RSA change. The three variables were considered and analyzed separately due to concerns about multicollinearity. We chose the RSA change score from baseline to the NA task as the DV because it was the variable that best captured the point at which group differences in RSA became apparent. Two approaches to examining indirect or mediational pathways have been discussed in recent years (e.g., MacKinnon, Lockwood, Hoffman, West, & Sheets, 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 that we did not have the recommended power because of a moderate sample size (MacKinnon et al., 2002), we chose to analyze the role of mediators using an intervening variable approach discussed by MacKinnon et al. (2000, 2002).

The first step in this process was to estimate the association between maternal cocaine use and the individual fetal growth measures using Linear Regression with the fetal growth measure as the criterion variable and maternal cocaine use as the predictor. Prenatal exposure to cocaine was significantly associated with BW ($Beta = -280.69$, $p < .001$) and BL ($Beta = -1.5$, $p < .001$). Maternal cocaine use did not account for significant variance in HC. Consequently, it was no longer considered as a potential mediator of the association between RSA change and maternal cocaine use during pregnancy. In the next step, the association between BW, BL, and the RSA change variable was estimated using Hierarchical Linear Regression with RSA change 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 (BW or BL) and maternal cocaine use during pregnancy. BL did not account for significance variance in RSA change and, consequently, was no longer considered as

potential mediators of the association between RSA change and maternal cocaine use during pregnancy. However, BW was significantly associated with RSA ($Beta = .003, p < .05$). The Product of Coefficients Test for the intervening variable effect was used to calculate the significance of any indirect effect (see MacKinnon et al., 2002). 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 was not significant, $z = 1.51$. Thus, BW did not mediate the association between prenatal exposure to cocaine and the RSA change.

The same procedure was used to evaluate maternal caregiving behavior (maternal negative affect, maternal sensitivity, and positive engagement) as potential mediators of the association between cocaine use during pregnancy and infant physiological regulation. Prenatal exposure to cocaine was associated with maternal negative affect (MNA: $Beta = -.23, p < .05$), but not with maternal sensitivity (MS) or positive engagement (PE). Infants who were prenatally exposed to cocaine had mothers who displayed higher levels of negative affect during the free play paradigm (see Tab. 1). In the next step, the association between NA and RSA change was estimated. Hierarchical Linear Regression was used with RSA as the criterion variable and NA and maternal cocaine use during pregnancy as the predictors. The intervening variable effect for MNA was not significant, $z = 1.39$. Thus, MNA did not mediate the association between prenatal exposure to cocaine and the RSA change.

Moderational Analyses

Next, we conducted exploratory analyses to examine if the association between cocaine exposure and autonomic regulation (RSA change from baseline to NA) was moderated by maternal caregiving behavior (MNA, PE, or MS) or fetal growth (BW, BL, or HC) using six separate regression analyses. The covariates described above were entered in the first step, followed by cocaine use and the moderator in the second step, and the interaction term in the third step. These analyses indicated no significant moderation by BW, BL, HC, MNA, PE, or MS.

Discussion

The primary focus of the present study was to examine physiological regulation in a sample of cocaine-exposed infants at 7 months of age. As predicted by the Polyvagal Theory (Porges, 1995, 1997, 1998), infants in the nonexposed group showed increases in HR and decreases in RSA (RSA suppression) during the negative affect task. This pattern of cardiac responsiveness is indicative of adaptive autonomic nervous system regulation for strong negative affect (Porges, 1995, 1997, 1998) and is consistent with earlier reports of decreased RSA during frustrating tasks and arm restraint (Stifter & Fox, 1990; Stifter & Jain, 1996). Thus, consistent with the Polyvagal theory (Porges, 1995, 1997, 1998), these infants inhibited the vagal brake, which resulted in increased sympathetic nervous system activity (i.e., increased HR). Consistent with our hypothesis, infants in the exposure group did not display RSA suppression during the negative affect tasks. Instead their RSA increased following the positive affect task and remained high throughout the remainder of the data collection procedure. The failure to suppress RSA in response to environmental challenge is consistent with previous findings that infants with regulatory disorders did not regulate (decrease) RSA from baseline to a task (DeGangi et al., 1991). Since other studies have indicated that there is a positive association between vagal regulation and both concurrent and future behavioral regulation during frustration (Calkins, 1997) and social tasks (Doussard-Roosevelt, Porges, Scanlon, Alemi, & Scanlon, 1997; Stifter & Corey, 2001; Suess & Bornstein, 2000), the findings of the current study suggest that infants who were

exposed to cocaine may be at risk for less adaptive behavioral regulation during environmental challenges.

Futhermore, these findings indicate that the association between heavy prenatal exposure to cocaine and failure to physiologically regulate during affect-eliciting procedures is not mediated or moderated by fetal growth or maternal caregiving behavior. However, both birthweight and negative maternal affect during interactions were unique predictors of RSA change during affect-eliciting tasks even after controlling for other fetal growth, gestational age, maternal alcohol, and cigarette use during pregnancy. Thus, these results suggest that prenatal exposure to cocaine is associated with both enhanced biological vulnerability and negative caregiving behaviors and along with prenatal cocaine exposure itself, this increased biological and environmental vulnerability may explain, in part, the failure of these infants to regulate, autonomically.

Infants who were prenatally exposed to cocaine also had heart rates that were marginally higher at baseline and significantly higher during the positive affect task than nonexposed infants. Both groups displayed a slight increase in HR during the negative affect eliciting task, however, there were no group differences in HR. Thus, exposed infants had a higher level of physiological arousal during periods of minimal environmental stimulation in response to slight environmental challenge. This difference was no longer evident during more moderate environmental challenge, perhaps due to a ceiling effect that prevented exposed infants from exhibiting more substantial increases in HR in response to the NA task.

Similar to previous studies that found group differences in baseline measures of RSA and other measures of heart rate variability during the neonatal period (Regalado et al., 1996, 2001; Schuetze & Eiden, 2006), we also found an association between prenatal exposure to cocaine and baseline RSA. Higher baseline RSA has been associated with increased positive and negative emotional reactivity (Fox, 1989; Stifter & Fox, 1990; Stifter, Fox, & Porges, 1989) and with behavioral reactivity (DiPietro & Porges, 1991; Gunnar, Porter, Wolf, Rigatuso, & Larson, 1995). Thus, our findings of significantly lower baseline RSA for exposed infants suggest increased autonomic reactivity. These findings are not limited to autonomic measures of reactivity. In fact, previous studies measuring the hypothalamic pituitary axis (HPA) have found group differences in baseline cortisol at this age among substance-exposed infants (Bendersky & Lewis, 1998b; Jacobson, Bihun, & Chiodo, 1999; Ramsey, Bendersky, & Lewis, 1996; Veira, Eiden, & Schuetze, 2004) which has been interpreted as increased stress reactivity (Bendersky & Lewis, 1998b; Gunnar & White, 2001). Thus, our findings lend additional support to the idea that cocaine-exposed infants have increased levels of stress reactivity, relative to nonexposed infants. It is important to note, however that our baseline measure here occurred after infants had been introduced to a new setting by novel research assistants, strapped into a car seat, hooked up to physiological data acquisition equipment and given a video to watch to induce a resting state, all of which may have been perceived as environmental stressors by the infant. Thus, this was not a true baseline measure obtained during minimal environmental stimulation but instead may reflect infant reactivity to these novel laboratory procedures and settings.

RSA generally displayed the reciprocal relations with HR that are predicted by the vagal brake model of cardiac activity for infants in the nonexposed groups. In fact, 65% of nonexposed infants showed the reciprocal relation characterized by increases in HR that were generally accompanied by decreases in RSA. However, for infants in the exposed group, the patterns of cardiac activity were generally nonreciprocal such that increases in HR were generally accompanied by increases in RSA. Only 35% of exposed infants displayed the typical reciprocal relationship between HR and RSA. Although other studies

have reported nonreciprocal cardiac patterns for human infants, they have almost universally reported a simultaneous *co-inhibition* of HR and RSA during tasks requiring highly focused attention (Richards & Casey, 1991; Suess & Bornstein, 2000). Lewis Hitchcock & Sullivan (2004), however, have reported simultaneous increases in HR and RSA among infants who also displayed increases in negative expressions of anger, sadness, and combinations of anger and sadness. They suggest that this “coactivation” of cardiac measures is indicative of stress rather than a single affective component. Thus, one interpretation of the increased HR and RSA seen among the exposed infants in this study is that they are experiencing heightened levels of physiological stress as the data collection procedure progressed. From an intervention perspective, the possibility that physiological stress is increased during environmental challenge suggests that we should carefully consider strategies for reducing stress among cocaine-exposed infants during periods of active stimulation.

Finally, it is important to note that there were no significant changes in HR or RSA during the positive affect task relative to baseline. Although some studies have found increases in RSA during positive affect tasks (Bazhenova, Plonskaia, & Porges, 2001), others have found that behavioral indicators of positive affect did not reliably correspond with changes in RSA (Weinberg & Tronick, 1996).

It is important to note one limitation of this study. First, although care was taken in the present 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 using the reliable TLFB interview, as well as analysis of medical records, 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.

Despite this limitation, the present findings are important because they provide additional support for the influence of prenatal exposure to cocaine on infant regulation. Not only, as previously reported, do these infants exhibit dysregulation during the neonatal period, but the current study provides evidence that prenatal exposure to cocaine is associated with physiological dysregulation during environmental challenge later in infancy. These findings may have implications for later development as deficits in the ability to respond appropriately to environmental demands have been associated with subsequent developmental problems.

Acknowledgments

The authors thank parents and infants who participated in this study and the research staff who were responsible for conducting numerous assessments with these families. Special thanks to Dr. Philip S. Zeskind for his collaboration on this study, to Dr. Amol Lele and Dr. Luther Robinson for collaboration on data collection at Women and Children's Hospital of Buffalo, and to Dr. Michael Ray for his collaboration on data collection at Sisters of Charity Hospital of Buffalo. This study was made possible by a grant from NIDA (1R01DA013190-01A2).

References

- Amaro H, Zuckerman B, Cabral H. Drug use among addicted mothers: Profile of risk. *Pediatrics*. 1989; 84:144–156. [PubMed: 2740164]
- Bard KA, Coles CD, Platzman K, Lynch AM. The effects of prenatal drug exposure, term status, and caregiving on arousal and arousal modulation in 8-week-old infants. *Developmental Psychobiology*. 2000; 36:194–212. [PubMed: 10737865]
- Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*. 1986; 51:1173–1182. [PubMed: 3806354]

- Baumgartner WA, Hill VA, Bland WH. Hair analysis for drugs of abuse. *Journal of Forensic Science*. 1989; 34:1433–1453.
- Bazhenova OV, Plonskaia O, Porges SW. Vagal reactivity and affective adjustment in infants during interaction challenges. *Child Development*. 2001; 72:1314–1326. [PubMed: 11699673]
- Beauchaine TP. Vagal tone, development, and Gray's motivational theory: Toward an integrated model of autonomic nervous system functioning in psychopathology. *Development and Psychopathology*. 2001; 13:183–214. [PubMed: 11393643]
- Bendersky M, Lewis M. Prenatal cocaine exposure and impulse control at 2 years. *Annals of the New York Academy of Sciences*. 1998a; 846:365–367. [PubMed: 9668426]
- Bendersky M, Lewis M. Arousal modulation in cocaine-exposed infants. *Developmental Psychology*. 1998b; 34:555–564. [PubMed: 9597364]
- Brandon TH, Copeland AL, Saper ZL. Programmed therapeutic messages as a smoking treatment adjunct: Reducing the impact of negative affect. *Health Psychology*. 1995; 14:41–47. [PubMed: 7737072]
- Brown J, Bakeman R, Coles CD, Sexon WR, Demi A. Maternal drug use during pregnancy: Are preterms and fullterms affected differently? *Developmental Psychology*. 1998a; 34:540–554. [PubMed: 9597363]
- Brown RA, Burges ES, Sales SD, Whitely JA, Evans DM, Miller I. Reliability and validity of a smoking timeline followback interview. *Psychology of Addictive Behaviors*. 1998b; 12:101–112.
- Brown JV, Bakeman R, Claire DC, Platzman KA, Lynch ME. Prenatal cocaine exposure: A comparison of 2-year-old children in parental and nonparental care. *Child Development*. 2004; 75:1282–1295. [PubMed: 15260878]
- Buss KA, Goldsmith HH. Fear and anger regulation in infancy: Effects on the temporal dynamics of affective expression. *Child Development*. 1998; 69:359–374. [PubMed: 9586212]
- Calkins SD. Cardiac vagal tone indices of temperamental reactivity and behavioral regulation in young children. *Developmental Psychobiology*. 1997; 31:125–142. [PubMed: 9298638]
- Calkins SD, Fox NA. The relations among infant temperament, security of attachment, and behavioral inhibition at twenty-four months. *Child Development*. 1992; 63:1456–1472. [PubMed: 1446562]
- Camm AJ, Malik M, Bigger JT, et al. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. *Circulation*. 1996; 93:1043–1065. [PubMed: 8598068]
- Clark R, Musick J, Scott F, Klehr K. The Mothers' Project Rating Scales of mother–child interaction. Unpublished manuscript. 1980
- Clark R. The Parent-Child Early Relational Assessment: A factorial validity study. *Educational & Psychological Measurement*. 1999; 59:821–846.
- DeGangi GA, DiPietro JA, Greenspan SI, Porges SW. Psychophysiological characteristics of the regulatory disordered infant. *Infant Behavior and Development*. 1991; 14:37–50.
- DiPietro JA, Porges SW. Vagal responsiveness to gavage feeding as an index of preterm stress. *Pediatric Research*. 1991; 29:231–236. [PubMed: 2034470]
- DiPietro JA, Porges SW, Uhly B. Reactivity and developmental competence in preterm and full-term infants. *Developmental Psychology*. 1992; 28:1–11.
- DiPietro JA, Suess PE, Wheeler JS, Smouse PH, Newlin DB. Reactivity and regulation in cocaine-exposed neonates. *Infant Behavior & Development*. 1995; 18:407–414.
- Doussard-Roosevelt JA, Porges SW, Scanlon JW, Alemi B, Scanlon K. Vagal regulation of heart rate in the prediction of outcome for very low birth weight preterm infants. *Child Development*. 1997; 68:173–186. [PubMed: 9179997]
- Eckberg DL. Human sinus arrhythmia as an index of vagal cardiac outflow. *Journal of Applied Physiology*. 1983; 54:961–966. [PubMed: 6853303]
- Eiden RD. Maternal substance use and mother-infant feeding interactions. *Infant Mental Health Journal*. 2001; 22:497–511.
- Emde, RN.; Gaensbauer, TJ. Modeling emotion in human infancy. In: Immelman, K.; Barlow, G.; Main, M.; Petrino, L., editors. *Behavioral Development: The Bielefeld Interdisciplinary Project*. New York: Cambridge University Press; 1981. p. 568-588.

- Feldman R, Greenbaum CW, Yirmiya N. Mother-infant affect synchrony as an antecedent of the emergence of self-control. *Developmental Psychology*. 1999; 35:223–231. [PubMed: 9923477]
- Fox NA. Psychophysiological correlates of emotional reactivity during the first year of life. *Developmental Psychology*. 1989; 25:364–372.
- Gable S, Isabella RA. Maternal contributions to infant regulation of arousal. *Infant Behavior & Development*. 1992; 15:95–107.
- Gawin FH, Ellinwood EH. Cocaine and other stimulants: Actions, abuse, and treatment. *New England Journal of Medicine*. 1988; 318:1173–1182. [PubMed: 3283549]
- Gingras JL, Weese-Mayer DE, Hume RF Jr, O'Donnell KJ. Cocaine and development: Mechanisms of fetal toxicity and neonatal consequences. *Early Human Development*. 1992; 31:1–24. [PubMed: 1486815]
- Goldsmith, HH.; Rothbart, MK. Laboratory Temperament Assessment Battery (Technical Manual). University of Wisconsin-Madison; 1996.
- Gottwald SR, Thurman SK. The effects of prenatal cocaine exposure on mother-infant interaction and infant arousal in the newborn period. *Topics in Early Childhood Special Education*. 1994; 14:217–231.
- Grossman P. Respiration, stress, and cardiovascular function. *Psychophysiology*. 1983; 20:284–299. [PubMed: 6408680]
- Grossman P, Karmaker J, Wieling W. Prediction of topic parasympathetic cardiac control using respiratory sinus arrhythmia: The need for respiratory control. *Psychophysiology*. 1991; 28:201–216. [PubMed: 1946886]
- Gunnar MR, Porter FL, Wolf CM, Rigatuso J, Larson MC. Neonatal stress reactivity: Predictions to later emotional temperament. *Child Development*. 1995; 66:1–13. [PubMed: 7497818]
- Gunnar, MR.; White, BP. Salivary cortisol measures in infant and child assessment. In: Singer, LT.; Zeskind, PS., editors. *Biobehavioral assessment of the newborn infant*. New York: Guilford Press; 2001. p. 167-189.
- Handler A, Kistin N, Davis F, Ferre C. Cocaine use during pregnancy: Perinatal outcomes. *American Journal of Epidemiology*. 1991; 133:818–825. [PubMed: 2021149]
- Jacobson SW, Bihun JT, Chiodo LM. Effects of prenatal alcohol and cocaine exposure on infant cortisol levels. *Development & Psychopathology*. 1999; 11:195–208. [PubMed: 16506530]
- James Long Company. IBI Analysis System reference guide. Caroga, NY: Author; 1999.
- Karmel BZ, Gardner JM. Prenatal cocaine exposure effects on arousal modulated attention during the neonatal period. *Developmental Psychobiology*. 1996; 29:463–480. [PubMed: 8809496]
- Katona PG, Jih F. Respiratory sinus arrhythmia: Noninvasive measure of parasympathetic cardiac control. *Journal of Applied Physiology*. 1975; 39:801–805. [PubMed: 1184518]
- Kopp CB. Regulation of distress and negative emotions: A developmental view. *Developmental Psychology*. 1989; 25:343–354.
- Krafchuk, E.; Tronick, E.; Clifton, R. Behavioral and cardiac responses to sound in preterm neonates varying in risk status and a hypothesis of their paradoxical reactivity. In: Field, TM.; Sostek, AM., editors. *Infants born at risk: Physiological and perceptual processes*. Grune & Stratton; 1983. p. 99-128.
- Lacey JI. The evaluation of autonomic responses: Toward a general solution. *Annals of the New York Academy of Science*. 1956; 67:125–163.
- LaGasse LL, Messinger D, Lester BM, Seifer R, Tronick EZ, Bauer CR, Shankaran S, Bada HS, Wright LL, Smeriglio VL, Finnegan LP, Maza PL, Liu J. Prenatal drug exposure and maternal and infant feeding behavior. *Archives of Disease in Childhood Fetal and Neonatal Edition*. 2003; 88:F391–F399. [PubMed: 12937043]
- Lester BM, Boukydis CFZ, García Coll CT, Hole WT. Colic for developmentalists. *Infant Mental Health Journal*. 1990; 11:321–333.
- Lewis M, Hitchcock DFA, Sullivan MW. Physiological and emotional reactivity to learning and frustration. *Infancy*. 2004; 6:121–143. [PubMed: 16718305]
- Littman A, Parmelee B. Medical correlation of infant development. *Pediatrics*. 1978; 61:474.

- MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the mediation, confounding, and suppression effect. *Prevention Science*. 2000; 1:173–181. [PubMed: 11523746]
- MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods*. 2002; 7:83–104. [PubMed: 11928892]
- Magura S, Freeman RC, Siddiqi Q, Lipton DS. The validity of hair analysis for detecting cocaine and heroin use among addicts. *International Journal of the Addictions*. 1992; 27:51–69. [PubMed: 1537640]
- Mayes LC, Bornstein MH, Chawarska K, Granger RH. Information processing and developmental assessments in 3-month-old infants exposed prenatally to cocaine. *Pediatrics*. 1995; 95:539–545. [PubMed: 7700755]
- Mayes LC, Bornstein MH, Chawarska K, Granger RH. Impaired regulation of arousal in three-month-old infants exposed to cocaine and other drugs. *Developmental Psychopathology*. 1996; 8:29–42.
- Mehta SK, Finkelhor RS, Anderson RL, Harcar-Sevik RA, Wasser TE, Bahler RC. Transient myocardial ischemia in infants prenatally exposed to cocaine. *Journal of Pediatrics*. 1993; 122:945–949. [PubMed: 8501575]
- Molitor A, Mayes LC, Ward A. Emotion regulation behavior during a separation procedure in 18-month-old children of mothers using cocaine and other drugs. *Development & Psychopathology*. 2003; 15:51–69.
- Nassogne, MC.; Evrard, P.; Courtoy, PJ. Selective direct toxicity of cocaine on fetal mouse neurons. Teratogenic implications of neurite and apoptotic neuronal loss. In: Harvey, JA.; Kosofsky, BE., editors. *Cocaine: Effects on the developing brain*. Annals of the New York Academy of Sciences. Vol. 846. New York: NY Academy of Sciences; 1998. p. 51-68.
- Oro AS, Dixon SD. Perinatal cocaine and methamphetamine exposure: Maternal and neonatal correlates. *Journal of Pediatrics*. 1987; 111:571–578. [PubMed: 3655989]
- Porges, SW. Respiratory sinus arrhythmia: Physiological basis, quantitative methods, and clinical implications. In: Grossman, P.; Janssen, K.; Vaitl, D., editors. *Cardiorespiratory and cardiosomatic psychophysiology*. New York: Plenum Press; 1986. p. 101-115.
- Porges, SW. Vagal tone: An automatic mediator of affect. In: Garber, J.; Dodge, KA., editors. *The development of emotion regulation and dysregulation*. Cambridge, England: Cambridge University Press; 1991. p. 111-128.
- Porges SW. Orienting in a defensive world: Mammalian modifications of our evolutionary heritage. A polyvagal theory *Psychophysiology*. 1995; 32:301–318.
- Porges, SW. Emotion: An evolutionary by-product of the neural regulation of the autonomic nervous system. In: Carter, CS.; Kirkpatrick, B.; Lederhendler, IL., editors. *Annals of New York Academy of Science*. 1997. p. 62-77. p. 807 The integrative neurobiology of affiliation
- Porges SW. Love: An emergent property of the mammalian autonomic nervous system. *Psychoneuroendocrinology*. 1998; 23:837–861. [PubMed: 9924740]
- Porges SW, Doussard-Roosevelt JA, Portales L, Greenspan S. Infant regulation of the vagal brake predicts child behavior problems: A psychobiological models of social behavior. *Developmental Psychobiology*. 1996; 29:697–712. [PubMed: 8958482]
- Ramsey DS, Bendersky MI, Lewis M. Effect of prenatal alcohol and cigarette exposure on two- and six-month-old infants' adrenocortical reactivity to stress. *Journal of Pediatric Psychology*. 1996; 21:833–840. [PubMed: 8990727]
- Regalado M, Schechtman V, Del Angel AP, Bean X. Sleep disorganization in cocaine-exposed neonates. *Infant Behavior and Development*. 1995; 18:319–327.
- Regalado M, Schechtman V, Del Angel AP, Bean X. Cardiac and respiratory patterns during sleep in cocaine-exposed neonates. *Early Human Development*. 1996; 44:187–200. [PubMed: 8654312]
- Regalado MG, Schechtman VL, Khoo MCK, Bean XD. Spectral analysis of heart rate variability and respiration during sleep in cocaine-exposed neonates. *Clinical Physiology*. 2001; 21:428–436. [PubMed: 11442576]
- Richards, JE. Attention in young infants: A developmental psychophysiological perspective. In: Nelson, CA.; Luciana, M., editors. *Handbook of developmental cognitive neuroscience*. Cambridge, MA: MIT Press; 2001. p. 321-338.

- Richards JE, Casey BJ. Heart rate variability during attention phases in young infants. *Psychophysiology*. 1991; 28:43–53. [PubMed: 1886963]
- Robbins TW. Arousal systems and attentional processes. *Biological Psychology*. 1997; 45:57–71. [PubMed: 9083644]
- Schuetze P, Eiden RD. The association between maternal cocaine use during pregnancy and physiological regulation in four to eight week old infants: An examination of possible mediators and moderators. *Journal of Pediatric Psychology*. 2006; 31:15–26. [PubMed: 15788714]
- Schore, AN. Affect regulation and the origin of self: The neurobiology of emotional development. Hillsdale, NJ: Lawrence Erlbaum Associates; 1994.
- Silvestri JM, Long JM, Weese-Mayer DE, Barkov GA. Effect of prenatal cocaine on respiration, heart rate and sudden infant death syndrome. *Pediatric Pulmonology*. 1991; 11:328–334. [PubMed: 1758757]
- Sobell MB, Sobell LC, Klajner F, Pavan D, Basian E. The reliability of a timeline method for assessing normal drinker college students' recent drinking history. *Addictive Behaviors*. 1986; 11:149–162. [PubMed: 3739800]
- Sroufe LA. The coherence of individual development: Early care, attachment, and subsequent developmental issues. *American Psychologist*. 1979; 34:834–841.
- Stifter CA, Braungart JM. The regulation of negative reactivity in infancy: Function and development. *Developmental Psychology*. 1995; 31:448–455.
- Stifter CA, Corey JM. Vagal regulation and observed social behavior in infancy. *Social Development*. 2001; 10:189–201.
- Stifter CA, Fox NA. Infant reactivity: Physiological correlates of newborn and 5-month temperament. *Developmental Psychology*. 1990; 26:582–588.
- Stifter CA, Fox NA, Porges SW. Facial expressivity and vagal tone in 5- and 10-month-old infants. *Infant Behavior and Development*. 1989; 12:127–137.
- Stifter CA, Jain A. Psychophysiological correlates of infant temperament: Stability of behavior and autonomic patterning from 5 to 18 months. *Developmental Psychobiology*. 1996; 29:379–391. [PubMed: 8732809]
- Suess PE, Bornstein M. Task-to-task vagal regulation: Relations with language and play in 20-month-old children. *Infancy*. 2000; 1:303–322.
- Suess PE, Porges SW, Plude DJ. Cardiac vagal tone and sustained attention in school-age children. *Psychophysiology*. 1994; 31:17–22. [PubMed: 8146250]
- Tronick EZ. Emotions and emotional communication in infants. *American Psychologist*. 1989; 44:112–119. [PubMed: 2653124]
- Tucker DM, Williamson PA. Asymmetric neural control systems in human self-regulation. *Developmental Psychology*. 1984; 91:185–215.
- Ungerer JA, Dolby R, Waters B, Barnett B, Kelk N, Lewin V. The early development of empathy: Self-regulation and individual differences in the first year. *Motivation & Emotion*. 1990; 14:93–106.
- Veira, Y.; Eiden, RD.; Schuetze, P. Prenatal cocaine exposure and infant stress response as measured by salivary cortisol. Paper presented at the biennial meeting of the International Society of Infant Studies; Chicago, IL. May. 2004
- Weinberg MK, Tronick EZ. Infant affective reaction to the resumption of maternal interaction after the still-face. *Child Development*. 1996; 67:905–914. [PubMed: 8706534]
- Wilder J. The law of initial value in neurology and psychiatry. *Journal of Nervous and Mental Diseases*. 1956; 125:73–86.

FIGURE 1.
Group differences in heart rate (HR) across conditions.

FIGURE 2.
Group differences in respiratory sinus arrhythmia (RSA) across conditions.

Table 1
Group Differences for Level of Cocaine Exposure

	Abstainers (<i>n</i> = 75)		Users (<i>n</i> = 79)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Maternal characteristics				
Age (years)**	28.71	5.60	31.31	5.62
Parity**	3.26	1.78	4.45	2.51
Socioeconomic status	1.49	.50	1.61	.49
Maternal Education (years)**	12.17	1.78	11.31	1.82
Prenatal care (# of visits) ⁺	15.61	7.55	13.1	8.91
Prenatal # of days cocaine/week**	0	0	.68	1.38
Prenatal # of cigarettes/week**	10.25	22.43	38.23	44.11
Prenatal # of standard drinks/week**	0.13	0.65	4.02	9.44
Prenatal # of binge drinking episodes/week**	.02	.10	0.35	1.07
Prenatal # of joints/week	1.09	6.35	1.40	4.47
Maternal positive engagement	3.83	.96	3.53	.99
Maternal sensitivity ⁺	4.21	1.55	3.91	1.11
Maternal negative affect [*]	4.52	.70	4.75	.40
Infant characteristics				
Gestational age [*]	39.45	1.22	38.78	1.84
Birthweight (g)**	3311.26	484.53	2994.13	564.02
Birthlength (cm)**	49.68	2.97	48.07	3.31
Head circumference at birth (cm)	33.52	1.33	33.32	2.37
OCS**	99.11	17.60	87.0	16.07

Notes: High scores on OCS reflect more optimal obstetric scores. Although there were no differences in maternal education in the full sample (as a result of matching for this variable), there were group differences for the subsample used in this analyses (consisting of infants who had full HR data at both time points). Attempts were made to group match for maternal age but because mothers who use cocaine during pregnancy are consistently older, we were not completely successful at full matching for this variable.

⁺ $p < .10$;

^{*} $p < 0.05$;

^{**} $p < 0.01$.

Table 2

Correlation Matrix for Mediator and Dependent Variables

	1	2	3	4	5	6	7	8
1. Birth weight (g)	—	—	—	—	—	—	—	—
2. Birth length (cm)	.62**	—	—	—	—	—	—	—
3. Head circumference (cm)	.48**	.15*	—	—	—	—	—	—
4. Maternal negative affect	.00	.01	.03	—	—	—	—	—
5. Positive engagement	.19*	.11	.15	.24**	—	—	—	—
6. Maternal sensitivity	.05	.02	.07	.53**	.54**	—	—	—
7. Heart rate—baseline	-.06	-.06	.13**	.17*	.10	-.12	—	—
8. Respiratory sinus arrhythmia (RSA)—baseline	-.04	.01	-.16*	-.14	-.07	-.18*	-.49**	—
9. RSA change	.17*	.12	-.06	.19*	.17*	.10	.01	-.13.

Note: Full correlation matrix is available upon request.

+ $p < .10$;

* $p < .05$;

** $p < .01$.

Table 3
Group Differences for Heart Rate Measures

	Abstainers		Users	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
RSA				
Baseline *	.027	.013	.021	.013
Positive affect task	.026	.017	.024	.016
Negative affect task	.021	.013	.023	.017
HR				
Baseline	135.88	11.33	139.37	12.59
Positive affect task *	136.13	13.37	140.31	12.21
Negative affect task	147.40	12.02	149.55	12.40
RSA change scores				
Baseline to positive affect task ⁺	-.001	.011	.003	.012
Baseline to negative affect task *	.005	.012	-.002	.019
HR change scores				
Baseline to positive affect task	.27	8.88	1.04	4.54
Baseline to NA	11.32	7.45	10.57	8.66

⁺ $p < .10$;

* $p < 0.05$;

** $p < 0.01$.