The effects of prenatal drug exposure, term status, and caregiving on arousal and arousal modulation in 8-week-old infants

Kim A. Bard[1], Claire D. Coles[2], Kathy A. Platzman, & Mary Ellen Lynch

Emory University School of Medicine

Department of Psychiatry

Human and Behavior Genetics Research Laboratory

Clinical Development and Applied Research Program

1256 Briarcliff Road, NE

Atlanta, GA 30306

and

[1]Department of Psychology, Emory University

532 Kilgo Circle, Atlanta, GA 30322

[2]Marcus Institute, a Division of the Kennedy-Krieger Institution at

Emory University

Running title: Arousal modulation in drug-exposed infants

Corresponding author:

Kim A. Bard, Department of Psychology, University of Portsmouth, King Henry

Building, King Henry I Street, Portsmouth, PO1 2DY Telephone: 44-01705-846332,

FAX 44-01705-846300, e-mail kim.bard@port.ac.uk

Abstract

Prenatal exposure to cocaine, as well as other drugs, has been linked with 'dysregulation', usually defined as problems in arousal and/or behavioral regulation. This study was designed to describe the physiological basis of 'dysregulation' as a function of prenatal cocaine-polydrug exposure and term status. Eight-week-old infants were selected because they are just developing the ability to modulate arousal. One hundred eighteen infants (23 preterm control, 27 preterm drug-exposed, 29 fullterm control, 39 fullterm drug-exposed) completed a protocol during which heart rate (HR) and respiratory rate (RR) were measured. Drug group differences were found in baseline, arousal (response to stress), and arousal modulation (recovery from stress). A hierarchical multiple regression analysis was conducted to determine the portion of variance attributable to postnatal caregiving environment, term status, and specific drug exposure. Term status accounted for significant variance in arousal (both RR and HR), and in arousal modulation (only RR). Prenatal exposure to cocaine contributed a significant amount of unique variance in HR arousal, whereas tobacco contributed significantly to HR arousal modulation. Prenatal drug exposure and preterm status contributed differently to 'dysregulation' as measured by physiological responses.

Key words: cardiac system, respiratory system, cocaine, prenatal drug exposure, prematurity, tobacco

The effects of prenatal drug exposure, term status, and caregiving on

arousal and arousal modulation in 8-week-old infants

Infants prenatally exposed to cocaine, and other drugs, are reported to exhibit

'dysregulation' in arousal. This 'dysregulation' in cocaine-exposed infants has been

variously described as under-aroused ('depressed') or over-aroused ('excitable': Lester,

Freier, & LaGasse, 1995), dysregulated in arousal-modulated attention (Karmel &

Gardner, 1996), more excitable with poorer state regulation (Tronick, Frank, Cabral,

Mirochnick, & Zuckerman, 1996), more irritable in response to novel stimulation (Mayes,

Bornstein, Chawarska, & Granger, 1995), 'disorganized' in behavioral state (DiPietro,

Suess, Wheeler. Smouse, & Newlin, 1995), having impaired regulation of arousal

(Mayes, Bornstein, Chawarska, Haynes, & Granger, 1996), less emotionally responsive

(Alessandri, Sullivan, Bendersky, & Lewis, 1995), and having more difficulty in self-

regulation (Chasnoff, Griffith, Freier, & Murray, 1992). It is difficult to understand what

these various dysfunctions in early regulatory ability may mean. Do these terms

describe the same or different problems? Are the problems attributed to cocaine

exposure based on dysfunctions of the same system? What are the developmental

consequences of these early dysfunctions? The current study was designed to

describe the physiological basis of arousal in order to better understand 'dysregulation'

in cocaine-polydrug exposed infants.

Three indicators of the physiological basis of arousal were used: baseline,

arousal (peak response) and arousal modulation (recovery from peak response).

Baseline physiology was measured for two reasons. First, baseline levels represent the

set-points of the systems, which may differ in preterms and fullterms, and/or may differ

as a function of drug exposure. Second, baseline values must be controlled when considering arousal responses, due to the Law of Initial Values (see Richards, 1980 for discussion). The term "arousal" indicates the physiological changes from baseline to peak responses. The term "arousal modulation" indicates recovery from the aroused state, and "good" arousal modulation is conceptualized as the return to baseline physiology at the end of the protocol.

It is important to identify those aspects of infants' early regulatory ability that may be affected by prenatal drug exposure. An assessment protocol was designed to be a moderately stressful situation for 8-week-old infants, and measured both Heart Rate (HR) and Respiratory Rate (RR). At the simplest level, arousal translates into increased HR and increased RR. HR acceleration in response to a stimulus indicates stress or arousal, whereas HR cardiac deceleration in response to a stimulus is indicative of attention (e.g., Berg & Berg, 1979; Richards, 1991. RR was included because of the reported links between (1) prenatal cocaine exposure and respiratory function (Brown, Bakeman, Coles, Sexson, & Demi, 1998: Silvestri, Long, Weese-Mayer, & Barkov, 1991), (2) premature birth and respiratory problems, and (3) perinatal drug exposure (especially tobacco) and respiratory problems. In terms of RR, increased stress or arousal results in increases in RR, however, there is no comparable decrease in RR that indicates attention, although RR does vary by behavioral state, e.g., RR is lower in quiet sleep than REM sleep (Regalado, Schechtman, Del Angel, & Bean, 1996). So, although the cardiac and respiratory systems are intricately linked, we expected to find that the systems reacted differently to moderate stress in 8-week-old infants who were prenatally exposed to drugs.

Arousal was studied in 8-week-old infants because basic physiological responses become organized around this age in typically developing infants. Throughout development, there are several distinct challenges faced by the infant and the caregiving environment. One of the first challenges is establishing homeostasis that is, regulating arousal (Kopp, 1982; Riese, 1987). When this challenge is met, infants can attend more effectively to external stimuli ('initial regulation': Greenspan & Lourie, 1981; Anders, 1989). In contrast, infants 'at-risk' may have difficulty in achieving this milestone.

Despite reports that prenatal exposure to cocaine and other drugs affect arousal and arousal modulation, further research is warranted because the basis for these effects is not clear due to a number of factors associated with cocaine and other drug use which may affect developmental outcomes (see Lutiger, Graham, Einarsor, & Koren, 1991 for a meta-analysis of confounding factors commonly attributed to adverse effects of prenatal cocaine exposure). These factors include 1); the indirect effects of polydrug use causing poor maternal health and prematurity 2) the direct effects of polydrug use on the fetus; and 3) the postnatal environment. So, it is important to consider these factors which may influence arousal and arousal modulation in association with substance use.

Maternal drug use has been shown to adversely affect the mothers' health and prenatal care, and to increase the risk for preterm birth (Kliegman, Madura, Kiwi, Eisenberg, & Yamashita, 1994). Each of these factors, especially preterm birth is associated with a number of negative developmental outcomes. It was decided to look at the effect of prenatal exposure to cocaine and other drugs on both fullterm and

preterm infants because few studies have included both in their samples and prematurity is known to influence arousal. Preterm status is a risk factor that may interact with prenatal drug exposure in an additive manner, suggesting that the preterm drug exposed infants would be the most 'dysregulated'. For example, cocaine/polydrug-exposed neonates exhibited increased irritability compared with controls, but more extreme irritability was found in infants that were both preterm and drug-exposed (i.e., Brown, Bakeman, Coles, Sexson, & Demi, 1998). In contrast, preterm status might protect the fetus from the deleterious effects of longer exposure to drugs (compared to the length of exposure found in the fullterm infants). In this case, it was expected that the preterm drug-exposed infants would be less dysregulated than fullterm drug-exposed (if drug exposure was more deleterious than prematurity). In addition, postnatal caregiving environment may interact with prematurity: Premature infants raised in nonoptimal environments are particularly at risk for poor developmental outcomes (e.g., Alyward, Pfeiffer, Wright & Verhulst, 1989).

Animal studies (reviewed in Spear, 1995) indicate that there are direct effects of prenatal exposure to cocaine on the central nervous system (e.g., cocaine blocks the re-uptake of neurotransmitters, dopamine, norepinephrine, and serotonin at the synapse), and on brain structures such as dendritic growth in the cerebellum (as reported by Willford, Hauser, & Barron, 1997). It is less clear that there are any long-term effects of cocaine on the cardiovascular system. There is an indirect effect of cocaine exposure mediated by a decrease in uterine blood flow resulting in hypoxia in the fetus. In fact, there is some controversy about the teratogenic effects of cocaine since recent well-controlled studies in human infants find minimal effects (e.g., Coles,

Platzman, Smith, James, & Falek, 1992: Lester, Freier, & LaGasse, 1995). Other drugs

are often used in conjunction with cocaine, including alcohol, marijuana, and tobacco,

and these drugs can also affect arousal. Concern about the adverse effects of cocaine,

in part, resulted from knowledge of negative direct effects of prenatal exposure to

teratogens, such as alcohol. Recent animal studies that combine exposure to cocaine

and alcohol, for example, indicate that there are interactive effects on dendritic growth,

at least in the cerebellum (e.g., Willford et al., 1997). In addition, prenatal exposure to

nicotine from maternal smoking has negative effects evident in the human newborn

(e.g., an increased number of abnormal reflexes, Coles et al., 1992). Thus, it is

important to control for the effects of prenatal exposure to other drugs (by experimental

design and/or by statistical means) because polydrug use is the rule for cocaine users.

The postnatal caregiving environment has a strong influence on the infant and the

infant's developing self-regulatory system from a very early age. The normal (or "good

enough") caregiving environment acts to facilitate the infant's ability to self-regulate through

the development of face-to-face interactions (Trevarthen, 1979, primary intersubjectivity)

and, later, of joint attention (secondary intersubjectivity: Trevarthen & Hubley, 1978),

achieving mutual regulation (e.g., Beeghly & Tronick, 1994). It may be the case that

consistent caregiver interactions are of primary importance in the integration of the social

with the self-regulatory systems, which begins around 4 weeks of age (e.g., Zeifman,

Delaney, & Blass, 1996). In the early months of life this social scaffolding may be more

salient than other regulatory systems for the infant (e.g., Coles, Bard, Platzman, & Lynch,

1999).

Thus, the current study was designed to investigate the effects of prenatal exposure to cocaine (in addition to alcohol, tobacco, and marijuana) and postnatal caregiving environment (interactional characteristics, such as regularity of caregiving routines, and caregiver stability) on physiological arousal and arousal modulation in preterm and fullterm 8-week-old infants. The hypotheses were that (1) Premature infants will exhibit higher arousal and poorer arousal modulation than fullterm infants; (2) Cocaine/polydrug-exposed infants will exhibit higher arousal and poorer arousal modulation than control infants; and (3) The effects of preterm birth and prenatal drug exposure will be additive, such that among the 4 groups, the preterm drug-exposed infants will be the most dysregulated.

In most samples, women who abuse cocaine differ from non-users in a number of characteristics, such as age and social support networks (e.g., Woods, Behnke, Eyler, Conlon, & Wobie, 1995). Moreover, it is typically the case that cocaine using mothers also use more alcohol, tobacco, and marijuana than non-cocaine using mothers. Finally, the postnatal caregiving environment for infants of substance abusing mothers is often dramatically different from that of non-users in terms of daily schedules and routines, stability in caregivers, and paternal involvement in the family. Any or all of these factors, in addition to prenatal exposure to cocaine, could be accounting for observed group differences in infant arousal and arousal modulation. Therefore, the fourth aim of the study was to conduct a hierarchical multiple regression analysis to explain the unique contributions of drug exposure, term status, and postnatal caregiving environment to variance in arousal and arousal modulation, while controlling for maternal characteristics (such as age, income, and social support networks).

Methods

Participants

The participants were 150 infants who began the 8-week protocol and their caregivers. All of these infants were initially recruited in the hospital at birth. Criteria for inclusion were 1) maternal age of at least 19 years; 2) no drug use other than cocaine, alcohol, tobacco, and marijuana; 3) adequate maternal health (e.g., no major medical conditions such as HIV infection, diabetes); 4) adequate infant health (e.g., no major infections, no major surgery, less than 30 days of oxygen); 5) planned bottle-feeding; and 6) English-speaking mothers (see Brown et al., 1998 for further details of the initial sample and the hospital sample from which the 8-week sample was drawn). Of the 150 infants who were recruited at 8-weeks, and had at least one measurement of heart rate or respiratory rate, a total of 118 completed the exam. Infants who finished and infants who did not finish the exam did not differ by drug group or by term status (see results on drop-outs).

Mothers were assigned to the drug group if they reported cocaine use during pregnancy, had a positive urine screen for cocaine, if their infants had a positive urine screen for cocaine, or if they reported alcohol use during pregnancy (> 2 oz AA/week). Mothers were assigned to the control group if none of these conditions were met. Medical records were used to determine drug use during pregnancy, and postpartum maternal and infant urine samples were analyzed for cocaine metabolites (enzyme-multiplex immunoassay technique, EMIT assay). Maternal self-reports consisted of Drug Checklist During Pregnancy (Coles, Brown, Smith, Platzman, Erickson, & Falek, 1991) and the Addiction Severity Index (ASI: McClelland, Luborsky, Cacciola et al.,

1985) administered either in the hospital and/or during the home visit within the first 30 days.   Perinatal urine screens were collected from most mothers and infants (92% of the user group and 96% of the nonusers). Most of the women with positive urine screens reported cocaine use (90%), and of the women in the user group with negative urine screens (34%), all reported cocaine or alcohol use during pregnancy. In the nonuser group, all of the mothers reported no cocaine use, which was confirmed by urine screens in 96% of the cases (urine was not collected in the remaining 4% of the cases).

Term status of infants was determined by the Ballard scoring system (Ballard, Novak, & Driver, 1979: for details see Brown et al., 1998). Sufficient information was obtained from infants' medical records to determine that preterm infants were free of major health problems (82% scored less than 2 on the Neonatal Medical Index: Korner, Stevenson, Forrest, Constantinou, Dimiceli, & Brown, 1994). Infants were classified as fullterm if they were at least 37 weeks GA at birth, or as preterm if they were between 28 and 36 weeks.

At 8-weeks, preterm infants' age was corrected to match the fullterms. The average Ballard score for the fullterms was 39 weeks which was selected as the 'standard'. The difference between the preterm infants' age at birth and 39 weeks was added to the infants' chronological age to arrive at the "corrected age" at which follow-up testing should occur. Infants were tested at 47 weeks conceptual age (8 weeks corrected age). For example, a preterm infant born at 35 weeks conceptual age would be tested at 12 weeks chronological age (difference between 39 and 35 is 4 weeks, added to chronological age of 8 weeks to determine "corrected age".)

Procedure

The protocol was designed to provide a variety of stimulation to the infant which increased in complexity and intrusiveness (i.e., from listening to sounds to whole body manipulations). The protocol employed the Bayley Scales of Infant Development (2nd Ed: BSID-II: Bayley, 1993) but it was slightly different from the clinical BSID-II in that: 1) the items were presented in a fixed order from single modality to multimodal in order to assess the infant's response to increasingly complex stimuli, and 2) a few items from the first version (BSID: Bayley, 1969) were included. The assessment lasted approximately 20 minutes and the examiner scored the infants' responses to obtain the typical BSID measures (i.e., the Mental Development Index (MDI) and the Motor Development Index (PDI) for each subject.

All infants were bottle-fed approximately 30 minutes before testing. In this sample, breast-feeding was an exclusion criteria because exposure to drugs postnatally might affect arousal. The test room was dimly lit. Leads were attached to the infant's thorax, and the infant was swaddled and placed in a prone position in a crib for approximately 10 minutes. Then the infant was turned supine, and the head was positioned and propped midline. The examiner soothed any infant who was fussy or crying prior to the baseline measurement using Brazelton & Nugent's (1995) suggested ordering of consoling techniques (from showing face to picking up, rocking, swaddling, and giving a pacifier to the infant). Physiology was measured at seven fixed and predetermined times. After one minute of calm behavior, the baseline physiological measurement was taken.   The second physiological measurement coincided with the presentation of an inanimate auditory stimulus (a rattle). The third physiological

measurement was taken upon the presentation of an inanimate visual stimulus (a red

ring). The fourth physiological measurement coincided with orientation to an animate

visual and auditory stimulus (the examiner's face and voice). The examiner talked to

the baby for 1 minute and then assessed the infant's reaction to the disappearance of

the face, and the infant's ability to follow a moving face. One minute later (with no

additional stimulation) the fifth physiological measurement was taken. Assessment of

the motor abilities of the infant was the next procedure. The sixth physiological

measurement was taken 1 minute after the completion of motor maneuvers in order to

allow the infant to recover from the actual movement. Thus, because the motor items

were the last items of the BSID-II, the sixth measurement was 1 minute following the

completion of the protocol. The final measurement was 4 minutes later, a total of 5

minutes after completion.

Infant Physiological and Behavioral Measurements. Heart rate (HR) in beats/minute

and respiratory rate (RR) in respirations/minute were measured using a Hewlett

Packard Cardiac Monitor (Model #788333) which provides a second by second display.

Physiological and behavioral state measures were taken at seven fixed and

predetermined times during the protocol (Figure 1). Behavioral state was measured on

a 7-point scale including states of 1) deep sleep, 2) light sleep, 3) drowsy, 4) quiet

awake, 5) active awake, 6) fussy/crying, and 7) vigorous crying.

Insert Figure 1 about here

Each measurement (of HR, RR, and behavioral state) consisted of four point

samples, the first of which was taken with the initial presentation of the item, and then at 15sec intervals thereafter for a total of 1 minute. For the analyses presented in this article, the four values were averaged at each measurement for HR and RR. For behavioral state, the equivalent 'average' was the predominant state within the one-minute interval, i.e., the state that occurred for 3 or 4 of the measurement points. If two states occurred equally often, then the most aroused state was used (i.e., rank ordering the states in arousal from asleep to awake to vigorous crying). All coding of behavioral state and averaging of HR and RR was conducted by the first author who was blind to the drug group and term status of each subject and had not interacted with any of the infants.

Assessment of Quality of Caregiving. While the infant was tested, caregivers were interviewed by a staff member to assess the quality of care (using an in-house-designed Structured Clinical Interview [SCI]: Coles, Platzman, Brown, Bard, & Lynch, 1997). Those aspects of the interview relevant to quality of caregiving (determined a priori) are listed in Table 1.

Insert Table 1 about here

Maternal Characteristics. Maternal education, age, and income were obtained during interviews at the hospital and at a home visit within 30 days after birth (see above). At the 8-week visit, the mother was interviewed regarding material resources, social support networks, and psychopathology.

The Family Resources Scale assessed material resources and consisted of 31 items (Dunst & Leet, 1988). The Social Support Scale consisted of 18 items (Dunst,

Trivette & Jenkins, 1988). A single summary score was obtained for each scale, which was the number of items which the respondent assessed as adequate or more than adequate. The SCL-90 is a 90-item self-report symptom inventory which assesses psychopathology (Derogatis, 1993). It yields nine primary symptom dimensions (e.g., paranoia, depression) and three global indices. The three global measures were highly correlated so one was chosen (the Global Severity Index: GSI) as a measure of maternal psychopathology.

Data summary

Infant physiologic and behavioral responses. Two constructs, arousal and arousal modulation, were of interest. **Arousal** was conceptualized in two ways: first, as highest level of arousal (i.e., the peak level of RR and HR) during the procedure and, second, as the timing of the peak level. Peak HR (and RR) was determined simply as the highest one-minute average HR (RR) during the course of the test. The second measurement of arousal was the period (of the 7 possible measurement periods) which contained the Peak HR (or Peak RR). **Arousal modulation** was conceptualized as the infant's ability to recover from an aroused state and was measured as the difference from baseline to the end of the protocol. The final measurement, taken after 5 minutes after the completion of the test, was thought to reflect recovery from the moderate stress of the protocol with a return to baseline physiological levels. For some analyses, the data were reduced from 7 measurements to 3 (baseline, peak, and end) in order to reflect the interest in arousal and arousal modulation. Reducing the number of measurement periods also increased the number of subjects because there were some missing data points.

Maternal Psychosocial Status. A Factor Analysis (principal components factoring, varimax rotation) was performed to reduce the large number of variables collected that characterized maternal background to one or two conceptually distinct factors. Two factors emerged (eigen values 2.0 and 1.4, respectively), **Resources** (accounting for 25% of the variance and composed of Family Resources, Family Support, and Global Severity Index of the SCL-90 which loaded negatively) and **SES** (accounting for 17% of the variance and composed of Education, Income, and Maternal age). Factor loadings for all included variables exceeded .50 and were standardized (to z-scores) and then averaged to form the two Factors (Resources and SES). These two factors were used in the Regression analyses to describe Maternal Psychosocial Status.

Quality of Caregiving. A Factor Analysis (principal components factoring, varimax rotation) was performed on the variables collected to assess Quality of caregiving. Two factors emerged accounting for 47% of the variance (with eigen values of 1.6 and 1.1, respectively): (1) **Instability**, which consisted of the Instability Cluster score from the SCI (Table 1 for the items assessed), whether the mother expected a lasting relationship with the father of the infant (loaded negatively), whether routine health care was planned, and whether the baby was planned (loaded negatively); and (2) **Neglect**, which consisted of involvement with Department of Family and Child Services (DFCS is the state child protection agency) and Caregiver Routine from the Structured Clinical Interview (SCI loaded negatively, see Table 1 for the items assessed). Factor loadings for all variables exceed .47and were standardized then

averaged to form two factors (Instability and Neglect) used in the regression analyses to describe the postnatal caregiving environment (i.e., Quality of Caregiving).

Statistical Analyses. Analyses with categorical data consisted of χ^2 with some groupings collapsed to minimize the number of cells with expected frequencies less than 5. Analyses with continuous data consisted of repeated measures ANOVA (begin, peak, end OR all 7 measurement periods) by term status (preterm, fullterm) and by drug group (drug-exposed versus control). If drug group differences were found, then hierarchical multiple regression analyses were planned to investigate the contribution of each of four constructs to explain the drug group differences. These constructs included Maternal Psychosocial Status, Quality of Caregiving, Term status (actual Ballard scores were used as a continuous measure), and Drug exposure (yes/no). Due to significant skew in the distribution of amounts of drug used in the sample, the amount of use was re-coded to a dichotomous variable (specifically, cocaine exposure/absence, alcohol exposure/absence, tobacco exposure/absence, and marijuana exposure/absence: see Brown et al., 1998). The first two constructs were designed a priori but included only those items arrived at through factor analyses (see above). The regression analyses were performed to ascertain whether exposure to specific drugs per se accounted for significant amounts of variance (after controlling for expected group differences in Maternal Psychosocial Status and Quality of Caregiving).

<div align="center">Results</div>

Maternal Characteristics

Background characteristics and frequency of substance use are shown in Table 2. Mothers of drug-exposed infants were significantly older than mothers of control

infants ($\underline{F}$(1,114)=15.39, $\underline{p}$<.01). Fewer mothers in the drug group than the control group graduated from high school (χ^2 (1)=6.40, $\underline{p}$<.05). Mothers in the drug group had more children than mothers in the control group ($\underline{F}$(1, 79)= 7.64, $\underline{p}$<.01). There were no drug group differences in race, income, or marital status. There were no term effects, nor any drug group by term interactions on any of these variables.

Insert TABLE 2 about here

Significant drug group effects were found in cocaine use ($\chi2$ (1)=58.9, p<.01), alcohol use ($\underline{F}$(1,107)=5.83, $\underline{p}$<.05), tobacco use (F(1,113)=33.11, $\underline{p}$<.01), and marijuana use ($\underline{F}$(1,110)=11.25, $\underline{p}$<.01). However, there were no differences between the preterm and fullterm groups on any of these measures, nor any interactions of drug group by term status.

There were no differences in the reported emotional health of mothers of drug-exposed infants and controls, nor between mothers of preterm and fullterms (Psychopathology measured by GSI of the SCL-90:Table 2). Mothers in the drug group reported a lower level of adequate material resources ($\underline{F}$(1,114)=4.45, $\underline{p}$<.05) and less adequate sources of support ($\underline{F}$(1,114)=4.96, $\underline{p}$<.05) compared with mothers in the control group.

Quality of caregiving

Significantly fewer drug-exposed infants were cared for by their biological mothers compared with control infants (Table 3). Significantly fewer drug-exposed infants had a male caregiver present in the household than did control infants.

Significantly fewer mothers of drug-exposed infants received prenatal care (71%)

compared with mothers of control infants (90%). The drug-exposed infants had

significantly more instability in caregiving compared with the control infants (as

measured by the Instability cluster from the SCI: $\underline{F}(1,109)=6.92$, $\underline{p}<.01$).   There was

significantly greater involvement by the drug group with DFCS compared with control

infants (χ^2 (1)= 9.67, $\underline{p}<.001$). There were no differences between the drug-exposed

and control infants, or between preterm and fullterm infants in Caregiver Routine.

Insert TABLE 3 about here

Infant Characteristics

At birth, infants differed by term status and by drug group in some growth

parameters (see Table 4). At 8-weeks corrected age, however, the only growth

parameter that differed was length: the infants prenatally exposed to drugs were shorter

than were the control infants (M=53.7 cm vs M=55.6 cm; $\underline{F}(1, 92)=9.13$, $\underline{p}<.01$). Age at

testing (M=56.6 days) was corrected for prematurity and did not differ by drug group nor

term status. There were no significant differences in the BSID-II scores by term status

(MDI: F(1, 103)=0.52, ns. PDI: F(1,103)= 0.10, ns) or by drug group (MDI:

F(1,103)=2.28, ns. PDI: F(1,103)=0.58, ns).

Insert TABLE 4 about here

Infant Physiological Responses

DROP-OUTS.

As in most experiments with very young human infants, a proportion of the initial sample was unable to complete the test protocol. One hundred and fifty infants began the physiological assessment but 21% of the sample ($\underline{n}$=32) dropped out prior to the end of the paradigm – some cried excessively and inconsolably whereas others slept and could not be aroused. There was not differential drop-out, based either on term status (11/61 preterms and 21/89 fullterms dropped out: χ^2 (2)=3.02, ns) or drug status (19/85 drug exposed and 13/65 controls dropped out: χ^2 (2)= 3.09, ns). There was an association of baseline HR with drop-out: Those who did not finish the exam had the lowest and most variable HR during the baseline period. An additional 18% ($\underline{n}$=27) exhibited some disruption during one or more periods but were able to finish the exam (recovers). The majority (61%) of the 8-week-old infants were sampled at each of the 7 periods (sustainers: $\underline{n}$= 91). There were no differences between sustainers and recovers in beginning HR, peak HR, or end HR and so these latter two groups were collapsed. There was no differential drop-out based on this new classification (i.e., drop-outs vs combined recovers and sustainers) on either drug group (χ^2 (1)= 0.16, ns) or term status (χ^2 (1)= 0.65, ns).

BEHAVIORAL STATE

The majority of the sample (78%) started the exam in an awake, noncrying state (10% were sleeping or drowsy and 12% were crying). A majority of the sample (75%) exhibited their Peak RR or HR response while crying (24% peaked with an awake state and 1% peaked with a drowsy state). A majority of the sample was not crying at the end of the exam (34% crying, 38% awake, and 28% asleep or drowsy). Preterms and

fullterms did not differ in behavioral state at any one of these periods, nor did drug

exposed and control infants. HR and behavioral state were significantly correlated

throughout the examination periods (with correlations ranging from .23 in Auditory to .59

at 1-min and 5-min Post). Because these variables were significantly correlated and

due to the continuous nature of HR and the categorical nature of behavioral state, the

remainder of the analyses was conducted with HR as the dependent variable. There

were no significant correlations between behavioral state and RR.

AROUSAL: Response to Stress

Timing of arousal.

HR changed significantly across the 7 periods (Figure 2: $F(6, 48)=2.18$, $p<.05$)

indicating that the experimental paradigm was effective in eliciting a mild to moderate

stress response. Simple contrasts revealed that, compared to baseline levels, HR was

significantly increased at the 5th period (after attention items), and at the 6th period (1-

min after completion of the protocol). Comparison of peak level of arousal revealed that

drug-exposed and control infants did not differ, and that preterm and fullterm infants did

not differ in Peak HR. However, there was a significant difference between groups in

the pattern of response (i.e., timing): The drug-exposed infants peaked earlier in the

exam than did the control infants ($\chi^2 (4)=10.35$, $p<.05$). The preterm infants did not

differ in timing compared with the fullterm infants. However, the analysis of the four

groups considered together revealed a significant interaction (Table 5: $\chi^2(9)=18.3$,

$p<.05$): Most preterm infants exhibited their peak HR during baseline or during the first

three attention periods (48% of the preterm drug and 39% of the preterm control

groups) as did most of the fullterm drug group (31%). Most of the fullterm controls

(50%), however, exhibited their peak HR during the final baseline period (5-min

recovery).

Insert FIGURE 2 and TABLE 5 about here

Respiratory Rate (RR)

There was a significant change in RR across the three periods, Beginning, Peak,

and End (F(2, 113)=155.98, p<.001: within-subjects contrasts revealed a significant

change from beginning to peak F(1, 114)=217.69, p<.001, but no difference between

beginning and end levels). There was a main effect of drug exposure. The group of

infants prenatally exposed to drugs had a higher RR compared with the control infants

across all three periods (Figure 2: F(1, 114)=4.50, p<.05). There was a main effect of

term status on RR. Preterm infants had a higher RR compared with fullterm infants

across all three periods (Figure 2: F(1,114)=7.25, p<.01). In this repeated measures

ANOVA, there were no interactions with change in RR. This means that although

baseline levels were different and peak levels were different, the RR change from

baseline to peak response was not different by group or by term status.

Insert FIGURES 3 and 4 about here

Heart Rate (HR)

HR exhibited a significant change from beginning HR, to peak HR, to end HR

(F(2,113)= 115.39, p<.001). There were no main effects of term status or of drug

group. Subsequent contrasts revealed that peak HR differed from baseline HR

(F(1,114)=177.76, p<.001), but that baseline HR did not differ from end HR. Moreover,

the change in HR from beginning to peak was different for preterms and fullterms

(within subject contrasts F(1, 114)=10.04, p<.01): Fullterms had a greater change

(M=19.6) than did preterms (M=12.53). There were no differences for drug-exposed

compared with control infants in HR change from beginning to peak.

AROUSAL MODULATION: Recovery from stress

Arousal modulation was the change in responding across intervals either from

baseline to end or from peak to end. There was a significant three-way interaction of

change in HR by term status by drug group (Figure 5: F(2, 113)=5.60, p<.01).

Subsequent contrasts revealed that the effect was found in comparisons with the End

period. The fullterm control infants and the preterm drug-exposed infants showed the

same pattern of response (higher end HR compared with beginning HR) which was

different from the pattern shown by the fullterm drug-exposed infant and the preterm

controls (a return in end HR to baseline HR levels).

Insert FIGURE 5 about here

INVESTIGATING DRUG GROUP DIFFERENCES: Hierarchical Multiple Regression

The analyses described in this section were designed to investigate the

contributions of the following constructs to the observed drug group differences entered

into the analysis in the following 4 steps: (1) indirect effects of substance abuse acting

through background Maternal Psychosocial Status (e.g., Resources, and SES see data

summary section for details) that might effect the developing fetus or infant; (2) indirect effects of substance abuse acting through the Quality of Caregiving (Instability and Neglect); (3) direct effects of preterm birth (Ballard score); and (4) direct effects of prenatal exposure to specific drugs (cocaine, alcohol, tobacco, and marijuana). Table 6 lists the unique variance (deltaR^2) at each step, the unstandardized partial regression coefficient (B) with standard error (SE), and the standardized partial regression coefficient (Beta) as each factor is entered in the model (with other variables in the set held constant).

Insert Table 6 about here

BASELINE HR: BASELINE RR.   Regressions on baseline physiology did not reveal significant effects for any of these factors.

AROUSAL (PEAK –BASELINE HR: PEAK RR). Preterm status contributed significantly to HR Arousal (5.6% of variance accounted for: $F(1,107)=6.42$, $p<.02$). Prenatal exposure to cocaine contributed an additional significant amount of unique variance to HR arousal (4.0%: $F(1,106)=4.75$, $p<.05$).

Preterm status contributed a significant proportion of unique variance to RR arousal (6.4%: $F(1,107)=7.49$, $p<.01$). There was no significant effect of cocaine on RR arousal. There were trends for contributions of alcohol ($t=1.79$, $p=.076$) and tobacco ($t=-1.74$, $p=.085$), but prenatal exposure to marijuana had no effect on RR arousal.

AROUSAL MODULATION (END-BASELINE HR: END RR). Prenatal exposure to cocaine contributed a marginally significant proportion of unique variance to HR

arousal modulation after controlling for differences in Maternal Psychosocial Status, Quality of Caregiving, and gestational age (2.7%: $\underline{F}$(1,106)=3.05, $\underline{p}$ =.08). Prenatal exposure to tobacco contributed significantly to HR arousal modulation ($\underline{t}$=-2.04, $\underline{p}$<.05).

Gestational age contributed a significant amount of unique variance to RR arousal modulation (5.3%: $\underline{F}$(1, 107)=6,01, $\underline{p}$≤.02). There were no significant effects of specific drugs on RR arousal modulation.

SUMMARY OF RESULTS

The first hypothesis was that preterm infants would exhibit higher arousal and poorer arousal modulation than fullterm infants. It was found that the physiological set-points of the preterms and fullterms were different: preterms did have a higher baseline RR than fullterms. But, after controlling for baseline RR, preterms did not have higher arousal (peak RR) than fullterms. Additionally, there were no differences between preterm and fullterms in arousal modulation (end RR), after controlling for baseline RR. A different pattern of term effects were found in the cardiac system. There were no difference in the set-point in HR: preterms and fullterms did not differ in baseline HR. There was a difference in arousal, after controlling for baseline HR, but surprisingly, fullterms exhibited higher arousal (peak HR) than preterms. There were no differences between preterms and fullterms in arousal modulation but there was an interaction of term status and drug group in arousal modulation (see below).

The second hypothesis was that drug-exposed infants would have higher arousal and poorer arousal modulation than non-exposed infants. In the respiratory system, differences were found in the set-point of the RR system: drug-exposed infants had a higher baseline RR than control infants. However, there were no group

differences in arousal (peak RR) or arousal modulation (end RR), after controlling for baseline levels. In the cardiac system, drug-exposed infants did not differ from control infants in baseline HR, or in arousal. There were no differences between drug-exposed and control infants in HR arousal modulation but there was an interaction between drug exposure and term status (see below).

The third hypothesis was that the effects of preterm status and drug exposure would be additive so that the preterm drug-exposed infants would exhibit the highest arousal and the poorest arousal modulation. In the respiratory system, the effects of drug exposure and term status were independent (each contributed to higher baseline RR rates but they were not additive). In the cardiac system, the effects were independent in arousal but interactive in arousal modulation. In arousal modulation, preterm drug-exposed had poorer arousal modulation than did the preterm controls, but fullterm drug-exposed had better arousal modulation than did fullterm controls. The level of recovery in HR was similar for the preterm drug-exposed and the fullterm control infants (these groups did not return to baseline). The fullterm drug-exposed and the preterm control infants exhibited "good" arousal modulation (i.e., these groups did return to baseline). Therefore, the hypothesis that preterm drug-exposed infants were the most dysregulated was rejected.

The final hypothesis was that drug group differences could be accounted for by the contribution of postnatal caregiving environment, term status, and other drug exposure in addition to cocaine exposure. In the respiratory system, there were no significant contributions of caregiving or drug exposure to arousal or arousal modulation, but term status contributed significantly to both arousal and arousal

modulation. In the cardiac system, term status and exposure to cocaine contributed to arousal, and exposure to tobacco contributed to arousal modulation, after controlling for the nonsignificant contributions of maternal psychosocial characteristics, and postnatal caregiving environment.

Discussion

The physiological systems of arousal and arousal modulation are affected differently by prenatal drug exposure. In the respiratory system of 8-week-olds, arousal was not affected by exposure to drugs after controlling for baseline levels, similar to the findings of Brown et al., (1996) for newborns. Exposure to other drugs, alcohol and tobacco that co-occur with cocaine, more strongly affected arousal (RR). HR arousal, in contrast, was significantly affected by exposure to cocaine, and only tobacco, among all the drugs, significantly affected HR arousal modulation. Neither Brown et al., (1998) nor Tuboku-Metsger, O'Shea, Campbell, Hulse, Bugg, & Jones (1996) found drug group differences in baseline HR or HR arousal when infants were tested at birth, but Silvestri et al. (1996) found drug group differences in HR at 2-weeks (note that the effect was only in fullterm infants and that cocaine-exposed infants had <u>lower</u> HR than non-exposed). It appears that prematurity is the major contributor to RR arousal and RR arousal modulation, but both prematurity and prenatal exposure to drugs contribute to HR arousal and HR arousal modulation.

Karmel & Gardner (1995), Regalado et al., (1995), and DiPietro et al., (1995) found cocaine exposed infants (4-week-olds, 2-week-olds, and newborns, respectively) exhibited higher arousal compared with non-exposed infants. It is interesting, however, that all note that the arousal and arousal modulation patterns which were atypical in the

drug-exposed neonate were more "mature" patterns typical of older non-exposed infants (Karmel, Gardner, & Freedland, 1996). This suggests that prenatal drug exposure may cause a dysregulation in the timing of what would otherwise be a developmentally appropriate response. In the current study, there were no differences in peak levels of arousal but differences in timing, with drug-exposed infants exhibiting peak arousal earlier in the exam than non-exposed infants. In this study, it is difficult to separate <u>when</u> the infants were most aroused, from <u>what</u> they were responding to with high levels of arousal. Additional experiments are needed to test this hypothesis because the structure of the protocol used in this study does not allow us to disentangle the issues of timing from the type of stimuli.

The control of the respiratory system and the cardiac system are closely linked; however, they are affected differently by preterm status and by prenatal drug exposure in 8-week-old infants. In 8-week-old infants of the current study preterms had higher baseline RR than fullterm infants, which was also found by Lester et al., (1996) for 4-week-old infants. In newborns, however, Brown et al., (1998) did not find a significant difference in baseline RR for preterm and fullterms. Perhaps, this is because both studies of older infants used corrected age (age corrected for prematurity) and the study of newborns tested the infants immediately after birth (for the fullterms but preterms were tested when medically stable which was a variable time after birth). However, there were no significant correlations of baseline RR with gestational age at birth, nor any correlation of baseline RR at 8-weeks with basal RR at birth. It is often the case that respiratory distress occurs in premature infants. In this sample, however, only healthy preterms were selected and still the degree of prematurity accounted for

significant variance in arousal and arousal modulation in the respiratory system. Silvestri et al. (1996) also found different types of cocaine polydrug effects on the HR and respiratory functioning of preterm and fullterm infants. These data suggest that prenatal cocaine exposure increases the maturity of lung function in preterm infants (e.g., Hanlon-Lundberg, Williams, Rhim, Covert, Mittendorf, & Holt, 1996). In contrast, prenatal cocaine exposure increases respiratory problems in fullterm infants (e.g., longer periods of apnea). It is concluded, therefore, that prenatal drug exposure affects the homeostasis of fullterms differently than that of the preterms.

The differences in baseline physiology are puzzling. Drug group differences and term differences were found in baseline RR but not in baseline HR. At 8-weeks, baseline RR was higher in the drug-exposed compared with the non-exposed whereas Regalado et al. (1996) did not find significant drug group differences in 2-week-old infants. Gingras, Feibel, Dalley, & Muellenaer (1995) found drug group differences in the number of awakings from sleep (in infants from 3 to 7 days of age), and DiPietro et al. (1995) found a greater number of state changes in cocaine-exposed newborns. Unlike Regalado et al. (1996) findings that RR varied with sleep state, we did not find a correlation between behavioral states and RR. In addition, there were no drug group differences in behavioral state at 8 weeks of age (most were typically awake during the entire protocol). Although there were drug group differences in baseline RR, once differences in maternal psychosocial factors, in maternal caregiving, and in term status were controlled, drug exposure did not contribute significantly to baseline physiology. A review of these studies suggest that cocaine may affect state organization involving sleep in neonates (specifically arousal from sleeping), whereas cocaine may affect

arousal from awake states by 8-weeks. It is interesting to note that in a follow-up study

of these infants when they were 24 months of age, significant drug group differences

were found in sleeping problems, such as problems getting to sleep and restlessness

during sleep, which are attributable to both caregiving (10.5% of the variance) and to

prenatal cocaine exposure (3.5%: Coles et al, in preparation). It appears that some of

the differences in findings across studies can be explained by the age at which infants

are assessed and their predominant behavioral state. These are important variables,

not only for infant assessments in general, but also when assessing drug exposure

effects on arousal and arousal modulation.

This study investigated arousal in 8-week-old infants who are just beginning to

regulate states of arousal. Thus, it is an interesting age to study the effects of drug

exposure on dysregulation. Previous studies of infants concentrated on newborns (birth

through 30 days), or 3-5 month-old infants, who have mastered the challenges of

regulating states and are facing new challenges (e.g., Kopp, 1982). There are few, if

any, studies of physiological responses as a function of cocaine exposure in older

infants or toddlers. Behaviorally based emotional responses to stressful situations

appear blunted in cocaine-exposed infants at older ages (e.g., 4-8 months Bendersky,

Alessandri, & Lewis, 1995). It is not known whether there were accompanying

physiological responses reflecting differential arousal (such as the low behavior-high

cortisol stress response seen in Japanese babies, Lewis, Ramsey & Kawakami, 1993).

Thus, it would be interesting to conduct a longitudinal study across the first year of life

of physiological responses in infants prenatally exposed to cocaine.

The protocol of the current study was moderately stressful, as indicated by

significant increases in both heart rate and respiratory rates, but there was not differential drop-out based on drug exposure. In contrast, at 3-months of age, Mayes et al. (1995) found that more cocaine-exposed infants dropped-out compared with non-exposed. In addition, Mayes et al. (1996) found cocaine-exposed infants were more aroused to initial stimulus presentation than were non-exposed 3-month-olds. Despite their increased arousal, the cocaine-exposed infants were not different from non-exposed infants upon repeated presentation of the stimulus. One possible interpretation of this effect is that cocaine-exposed infants experience greater arousal than non-exposed infants, and most (those who finished), by 3-months of age, have developed arousal modulation techniques to successfully deal with their increased arousal. In the current study, the fullterm drug-exposed infants did exhibit arousal modulation (HR returned to baseline levels) and it was surprising that the fullterm control group did not exhibit arousal modulation. It should be highlighted that, in this study, the fullterm control group did not modulate arousal, raising questions about our understanding of what is meant by ~good~ arousal modulation in the fullterm cocaine and preterm control infants. There are areas of functioning that have been described as "better" or "more mature" in cocaine-exposed infants (e.g. faster visual processing, Jacobson, Jacobson, Sokol, Martier, & Chiodo, 1996) but we think that, in this case, it is the age-typical reliance on caregivers that is responsible for the fullterm control infants being most distressed by the post-test.

It was predicted that quality of caregiving would significantly impact arousal and arousal modulation. Specifically, the hypothesis was that the interactive effect of term status and drug group on HR arousal modulation occurred through the indirect pathway

of quality of caregiving. In the immediate postnatal period, premature infants thrive with less stimulation compared with the optimal level for fullterm infants (e.g., Gorski, 1983). Mothers who abuse substances might engage in less stimulation of their infants than do non-substance abusing mothers (the strongest evidence for this statement is the increased incidence of infant mortality in the drug-exposed group compared with the non-exposed group, due to neglect rather than abuse: Coles, unpublished manuscript. Note, however, that when mothers are responsive they may be comparable to non-substance using mothers in behavior, see for example, Bendersky & Lewis, 1998). Thus, the hypothesis was that this could be one pathway whereby the preterm drug-exposed infants would exhibit homeostasis that is similar to the fullterm controls. However, the multiple regression analysis did not reveal a significant contribution of Quality of Caregiving to HR arousal modulation, so this hypothesis must be rejected. A second speculation involves the causes for prematurity. It could be that drug-exposed infants born prematurely differ from infants born prematurely for endogenous reasons. From animal studies, it is know that the most deleterious effects of prenatal cocaine exposure occur in the third trimester (reviewed by Spear, 1995). Thus, it might be the case that arousal and arousal modulation in premature drug-exposed infants differs from that of fullterm drug-exposed infants due to a shorter duration of exposure to cocaine.

It is possible to interpret the findings in both arousal and arousal modulation as drug group differences in reactivity to social stimuli. The drug group exhibited peak arousal (HR) after orientation to the social stimulus. In a study of 8-week-old infants, Coles et al. (1999) found drug-exposed infants exhibit HR accelerations to a social

stimulus but control infants exhibit HR decelerations indicative of focused attention to a social stimulus. There were no drug group differences in HR patterns to nonsocial stimuli. Both studies found that cocaine was significantly related to HR arousal. In contrast to the current study, however, Coles et al. found that the quality of caregiving accounted for an additional significant amount of the variance in HR arousal (i.e., response to social stimuli). The differences in arousal modulation may relate to the reaction of a lack of social interaction: the fullterm control infants, among the four groups, exhibited their peak arousal (HR) in response to the absence of social stimulation (5 minutes after the cessation of the exam). Both the preterm control infants and the fullterm drug-exposed infants were able to recover from stress when left alone for 5 minutes. In the current study, neither arousal nor arousal modulation was related to postnatal caregiving. More research is clearly needed to tease apart the mechanisms. It is likely that the caregiving environment has an impact on the types of stimuli that infants find arousing (or interesting) and on the manner by which infants recover from stress. In contrast, prematurity and prenatal drug exposure impact baseline physiology, and the levels of arousal and arousal modulation.

Prenatal cocaine exposure may result in subtle differences in development. Cocaine appears to act earliest on endogenous neuroregulatory capacity, perhaps imparting physiological irritability (Brown et al., 1998; Lester et al., 1995) and increased arousal from sleep at birth (DiPietro et al.,1995; Gingras et al., 1995). Cocaine and postnatal caregiving may already interact by 2-months of age, thereby altering neurophysiological modulation. Recent research in the development of the opioid system suggests that social stimuli begin to be an integral part of the regulatory system

as early as 4 weeks of age (Zeifman et al., 1996), and opioid receptor binding is altered

by cocaine (e.g., Spear, 1995). So studies that report cocaine effects are often indirect,

via pathways of maternal health or quality of caregiving (e.g., Black, Schuler, & Nair,

1993: Vogel, 1997) are probably helping to explain 'dysregulation' in the sense of the

integration of social supports with self-regulation. By 3-months of age, the infant's

neurophysiological modulation has become integrated with the regulatory supports of

the caregiving environment (e.g., Bigleow, 1997). Neurophysiological modulation may

lay the foundation for self-regulatory abilities during emotionally stressful situations later

in life (Kopp, 1982). It is likely that the combination of prenatal cocaine exposure

(affecting physiological regulation) and postnatal environment (affecting the integration

of social supports for regulation) leads to the reports of "dysregulation" in social and

emotional behavior in older infants and children.

Notes

References

Alyward, G.P., Pfeiffer, S.I., Wright, A. & Verhulst, S.J. (1989). Outcome studies of low birth weight infants published in the last decade: A metaanalysis. Journal of Pediatrics, 115, 515-520.

Alessandri, S.M., Sullivan, M.W., Bendersky, M., & Lewis, M. (1995). Temperament in cocaine-exposed infants. In M. Lewis & M. Bendersky (Eds.), Mothers, Babies, and Cocaine: The Role of Toxins in Development (pp. 273-286). Hillsdale, NJ: Lawrence Erlbaum & Associates, Inc.

Ballard, J.L.; Novak, K.K.; Driver, M.A.: A simplified score for assessment of fetal maturation of newly born infants. Journal of Pediatrics. 95, 69-74, 1979.

Bayley, N. (1993). Bayley Scales of Infant Development (2nd Ed). Psychological Corporation. San Antonio, TX: Harcourt Brace and Company.

Bayley, N. (1969). Bayley Scales of Infant Development. The Psychological Corporation. San Antonio, TX: Harcourt, Brace, & Co.

Beeghly, M., & Tronick, E. Z. (1994). Effects of prenatal exposure to cocaine in early infancy: Toxic effects on the process of mutual regulation. Infant Mental Health Journal, 25, 158-174.

Bendersky, M. & Lewis, M. (1998). Arousal modulation in cocaine-exposed infants. Developmental Psychology, 34, 555-564.

Bendersky, M., Alessandri, S.M., & Lewis, M. (1996). Emotions in cocaine-exposed infants. In M. Lewis & M. W. Sullivan (Eds.), Emotional Development in Atypical Children (pp. 89-108). Hillsdale, NJ: Lawrence Erlbaum & Associates, Inc.

Berg, W.K. & Berg, K.M. (1979). Psychophysiological development in infancy: State, sensory function and attention. In J. Osofsky (Ed.).Handbook of infant development (pp. 283-343). New York, NY: Wiley & Sons.

Black, M., Schuler, M., & Nair, P. (1993). Prenatal drug exposure: Neurodevelopmental outcome and parenting environment. Journal of Pediatric Psychology, 18, 605-620.

Brazelton, T.B. & Nugent, J. K. (1995). Neonatal Behavioral Assessment Scale (3rd ed.). London, UK, Mac Keith Press.

Brown, J.V., Bakeman, R., Coles, C.D., Sexson, W.R., & Demi, A.S. (1998). Maternal drug use during pregnancy: Are preterms and fullterms affected differently? Developmental Psychology, 34(3), 540-554.

Chasnoff, I.J., Griffith, D.R., Freier, C., & Murray, J. (1992). Cocaine/polydrug use in pregnancy: Two-year follow-up. Pediatrics, 89, 284-289.

Coles, C.D., Brown, R.T., Smith, I.E., Platzman, K.A., Erickson, S., & Falek, A. (1991). Effects of prenatal alcohol exposure at school age: I. Physical and cognitive development. Neurotoxicology and Teratology, 13(4), 357-367.

Coles, C.D., Bard, K.A., Platzman, K.A., Lynch, M.E. (1999). Attentional responses at 8 weeks in prenatally drug-exposed and preterm infants. Neurotoxicology and Teratology, 21, 527-537.

Coles, C.D., Platzman, K.A., Smith, I., James, M.E., & Falek, A. (1992) Effects of cocaine and alcohol use in pregnancy on neonatal growth and neurobehavioral status. Neurotoxicology and Teratology, 14, 23-33.

Derogatis, L.R. (1993). Symptom Checklist-90-R. Minneapolis, MN: National Computer Systems.

DiPietro, J.A., Suess, P.E., Wheeler, J.S., Smouse, P.H., & Newlin, D.B. (1995). Reactivity and regulation in cocaine-exposed neonates. Infant Behavior and Development, 18, 407-414.

Dunst, C.J., & Leet, H.E. (1988). Family resource scale. In C.J. Dunst, C.M. Trivette, A.G. Deal (Eds.), Enabling and Empowering Families: Principles and Guidelines for Practice (pp. 139-141). Cambridge, MA: Brookline Books.

Dunst, C.J., Trivette, C.M., & Jenkins, V. (1988). Family support scale. In C.J. Dunst, C.M. Trivette, A.G. Deal (Eds.), Enabling and Empowering Families: Principles and Guidelines for Practice (pp. 155-157). Cambridge, MA: Brookline Books.

Emde, R. & Buchsbaum, H.K. (1989) Toward a psychoanalaytic theory of affect: II. Emotional development and signaling in infancy. In S.I. Greenspan & G.H. Pollock (Eds). The course of life, Vol 1: Infancy, pp. 193-227. Madison, CT: International Universities Press.

Gingras,J.L., Feibel, J.B., Dalley, & Muelenaer, A. (1995). Maternal polydrug use including cocaine and postnatal infant sleep architecture: Preliminary observations and implications for respiratory control and behavior. Early Human Development, 43, 197-204.

Gorski, P.A. (1983). Premature infant behavioral and physiological responses to caregiving interventions in the Intensive Care Nursery. In. J. Call (Ed.), Frontiers in Infant Psychiatry (pp. 256-263), New York, NY: Basic Books.

Greenspan, S.I., & Lourie, R.S. (1981). Developmental structuralist approach to

classification of adoptive and pathologic personality organizations: Infancy and early childhood. American Journal of Psychiatry, 138, 725-735.

Jacobson, S. W., Jacobson, J. L., Sokol, R. J., Martier, S. S., & Chiodo, L. M. (1996). New evidence for neurobehavioral effects of in utero cocaine exposure. Journal of Pediatrics, 129, 581-590.

Karmel, B.Z., & Gardner, J.M. (1996). Prenatal cocaine exposure effects on arousal-modulated attention during the neonatal period. Developmental Psychobiology, 29(5), 463-480.

Karmel, B.Z., Gardner, J.M., & Freedland, R.L. (1996). Arousal-modulated attention at four months as a function of intrauterine cocaine exposure and central nervous system injury. Journal of Pediatric Psychology, 21(6), 821-832.

Kliegman, R.M., Madura, D., Kiwi, R., Eisenberg, I., & Yamashita, T. (1994). The relationship of maternal cocaine use to the risks of prematurity and low birth weight. Journal of Pediatrics, 124, 751-756.

Kopp, C.B. (1982). Antecedents of self-regulation: A developmental perspective. Developmental Psychology, 18, 199-214.

Korner, A., Stevenson, D.K., Forrest, T., Constantinou, J.C., Dimiceli, S., & Brown, B.W., Jr. (1994). Preterm medical complications differentially affect neurobehavioral functions: Results from a new neonatal medical index. Infant Behavior and Development, 17, 32-43.

Lester, B.M., Boukydis, C.F. Z., & LaGasse, L. (1996). Cardiorespiratory reactivity during the Brazelton Scale in term and preterm infants. Journal of Pediatric Psychology, 21, 771-783.

Lester, B.M., Freier, K., & LaGasse, L. (1995). Prenatal cocaine exposure and child outcome: What do we really know? In M. Lewis & M. Bendersky (Eds.), Mothers, Babies, and Cocaine: The Role of Toxins in Development (pp. 19-39). Hillsdale, NJ: Lawrence Erlbaum & Associates, Inc.

Lewis, M., Ramsay, D.S., & Kawakami, K. (1993). Differences between Japanese and Caucasian American infants in behavioral and cortisol response to inoculation. Child Development, 64, 1722-1731.

Lutiger, B., Graham, K., Einarson, T.R. & Karen, G. (1991). Relationship between gestational cocaine use and pregnancy outcome: A meta-analysis. Teratology, 44, 405-414.

Mayes, L. C. (1995). Substance abuse and parenting. In M. H. Bornstein (Ed.). The Handbook of Parenting, Vol. 4 Applied and Practical Parenting. (pp. 101-125). Mahwah, N. J.: Lawrence Erlbaum Associates, Inc.

Mayes, L.C., Bornstein, M. H., Chawarska, K., & Granger, R. H. (1995). Information processing and developmental assessments in three month olds exposed prenatally to cocaine. Pediatrics, 95(4), 539-545.

Mayes, L.C., Bornstein, M.H., Chawarska, K., Haynes, O.M., & Granger, R.H. (1996). Impaired regulation of arousal in 3-month-old infants exposed prenatally to cocaine and other drugs. Development and Psychopathology, 8, 29-42.

McClellan, A.T., Luborsky, L., Woody, G.E., O'Brien, C.P. (1980). An improved validation instrument for substance abuse patients: The Addiction Severity Index. Journal of Nervous and Mental Disease, 168(1), 26-33.

Platzman, K.A., Bard, K.A., Coles, C.D., Brown, J.V., & Lynch, M.E. (submitted). Assessment of the caregiving environment and infant functioning in polydrug families: Use of a Structured Clinical Interview. Infant Mental Health Journal.

Regalado, M.G., Schechtman, V.L., Del Angel, A. P., & Bean, X.D. (1996). Cardiac and respiratory patterns during sleep in cocaine-exposed neonates. Early Human Development, 44, 187-200.

Richards, J.E. (1980). The statistical analysis of heart rate: A review emphasizing infancy data. Psychophysiology, 17,153-166.

Riese, M.L. (1987). Temperamental stability between the neonatal period and 24 months. Developmental Psychology, 23(2), 216-222.

Silvestri, J.M., Long, J.M., Weese-Mayer, D.E., & Barkov, G.A. (1991). Effect of prenatal cocaine respiration, heart rate, and sudden infant death syndrome. Pediatric Pulmonology, 11, 328-334.

Spear, L. (1995). Neurobehavioral consequences of gestational cocaine exposure: A comparative analysis. In C. Rovee-Collier & L.P. Lipsitt (Eds.), Advances in Infancy Research, Vol 9. Norwood, N.J.: Ablex Publishing Co.

Trevarthen, C. (1979). Communication and cooperation in early infancy: A description of primary intersubjectivity. In M. Bullowa (Ed), Before speech: The beginning of interpersonal communication, pp.321-347.

Trevarthen, C., & Hubley, P. (1979). Secondary intersubjectivity: Confidence, confiding, and acts of meaning in the first year. In A. Lock (Ed), Action, gesture, and symbol: The emergence of language. New York: Academic Press.

Tronick, E., Frank, D.A., Cabral, H., Mirochnick, M., & Zuckerman, B. (1996).

Late dose-response effects of prenatal cocaine exposure on newborn neurobehavioral performance. Pediatrics, 98, 76-83.

Tuboku-Metzger, A.J., O'Shea, J.S., Campbell, R.M., Hulse, J.E., Bugg, G.W., & Jones, D.W. (1996). Cardiovascular effects of cocaine in neonates exposed prenatally. American Journal of Perinatology, 13, 1-4.

Vogel, G. (1997). Cocaine wreaks subtle damage on developing brains. Science, 278, 38-39.

Willford, J.A., Hauser, K.F., & Barron, S. (1997). The effects of neonatal exposure to alcohol, cocaine or alcohol/cocaine on dendritic spine density in the cerebellum. Alcoholism: Clinical and Experimental Research, 21, 85a (abstract).

Woods, N.S.; Behnke, M.; Eyler, F.D.; Conlon, M.; Wobie, K.: Cocaine use among pregnant women: Socioeconomic, obstetrical, and psychological issues. In: Lewis, M.; Bendersky, M., Eds. Mothers, babies, and cocaine: The role of toxins in development. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.; 1995:305-332.

Zeifman, D., Delaney, S., & Blass, E.M. (1996). Sweet taste, looking, and calm in 2- and 4-week-old infants: The eyes have it. Developmental Psychology, 32, 1090-1099.

Table 1: Items in the Routine and Instability Clusters from the Structured Interview

used to quantify Quality of Caregiving

Items in the Caregiver Routine Cluster	Score
1. Number of Daily Activities fewer than average ($\underline{M}$= 2)	Yes=1
2. Number of Bottles fewer than average ($\underline{M}$=4.35)	Yes=1
3. Number of Diaper Changes fewer than average ($\underline{M}$=5)	Yes=1
4. Baby always held during feeding	No=1
5. Caregiver recognizes "hungry " cry	No=1
6. Baby notices sounds	No=1
7. Baby looks at things	No=1
8. Family responds positively to baby's cries	No=1
9. Baby can be comforted easily	No=1
10. Baby has learned new things	No=1

Items in Parenting Instability Cluster	Score
1. Preparations made for baby prenatally	No=1
2. Baby has necessary supplies/equipment	No=1
3. Adult Male in household	No=1
4. Baby in 'daycare' more than 40 hours per week	Yes=1
5. Mother has help with baby	No=1
6. Baby has more than 2 regular caregivers	Yes=1
7. Baby separated from primary caregiver (> 48 hours)	Yes=1
8. Baby fed significantly less than average ($\underline{M}$=19.7oz)	Yes=1
9. Baby sleeps significantly more or less than average	Yes=1
10. Respondent is biological mother, father, grandmother, or foster parent	No=1
11. If not living with mother, sees mother regularly	No=1
12. Baby has own bed	No=1
13. Baby has frequent falls/injuries	Yes=1

Table 2: Maternal characteristics (Mean $\pm$ SD or % of group) and Drug use (n=118)

Maternal Characteristics	Preterm Control (n = 23)	Preterm Drug (n = 27)	Fullterm Control (n = 29)	Fullterm Drug (n = 39)
Maternal Age (yrs)**	26.6 (6.1)	31.0 (5.9)	26.4 (5.1)	29.6 (4.0)
Education (at least High School grad)*	70%	52%	66%	38%
Income (percent<$300/mo)	52%	73%	66%	54%
Marital Status (percent unmarried)	78%	96%	90%	90%
Ethnicity (%African-Am)	96%	100%	97%	97%
Parity (# prev. births)**	2.44 (1.2)	3.50 (2.01)	2.89 (1.4)	3.70 (1.3)
Global Psychopathology (GSI T score)	52.7 (11.2)	54.3 (11.9)	53.2 (9.7)	55.9 (10.6)
Social Support*	4.9 (2.9)	3.1 (2.6)	4.3 (2.9)	3.8 (2.9)
Family Resources*	20.4 (5.4)	17.6 (5.7)	18.9 (5.9)	17.2 (5.7)
Reported Drug Use **Cocaine****				
Daily Use	0%	15%	0%	23%
Weekly Use	0%	27%	0%	38%
Monthly Use	0%	19%	0%	13%
Alcohol (oz AA/wk)*	0.02 (0.11)	3.75 (6.80)	0	5.17 (15.46)
Tobacco (#cigarettes/wk)**	18.56 (44.50)	55.67(43.60)	7.17 (19.5)	62.80 (54.01)
Marijuana (# joint/wk)**	0	0.5 (0.94)	0	0.16 (0.46)

*p<.05 **p<.01

Table 3: Quality of Caregiving variables for drug-exposed and control groups.

Parenting Instability

	Drug	Control	Statistics
Instability Cluster*($\underline{M} \pm$ SD)	2.87 $\pm$1.59	2.08 $\pm$1.37	$\underline{F}$(1,109)=6.92, $\underline{p}$<.01
Mom is primary caregiver*	77%	95%	χ^2(1)=6.69, $\underline{p}$<.01
Male caregiver present*	42%	62%	χ^2(1)=4.44, $\underline{p}$<.05
Received prenatal care*	75%	96%	χ^2(1)=8.62, $\underline{p}$<.01
Lasting relationship with male*	52%	71%	χ^2(1)=3.85, $\underline{p}$<.05
Baby was planned*	7%	31%	χ^2(1)=9.20, $\underline{p}$<.01

Parental Neglect

	Drug	Control	Statistics
Routine Cluster (M+SD)	1.68$\pm$1.10	1.40 $\pm$1.18	$\underline{F}$(1,109)=2.21, ns
Protective Services (DFCS)*	17%	0%	χ^2(1)=9.67, $\underline{p}$<.01
Thing baby has learned* ($\underline{M}$)	2.33$\pm$1.2	3.03$\pm$1.49	$\underline{F}$(1,109)=6.55, $\underline{p}$<.05
Types of daily activities* (M)	3.30$\pm$1.76	4.04$\pm$1.70	$\underline{F}$(1,109)=4.55, $\underline{p}$<.05

* Drug group differences

Table 4: Infant characteristics at birth and at 8-week visit (N=118): Mean (and SD)

At Birth	Preterm Control (n = 23)	Preterm Drug (n = 27)	Fullterm Control (n = 29)	Fullterm Drug (n = 39)
Gestational age+	33.7 (1.8)	33.8 (2.0)	39.7 (1.3)	39.2 (1.2)
Apgar 1min+	6.36 (2.34)	6.5 (2.21)	8.08 (1.47)	8.44 (1.80)
Apgar 5min+	7.77 (1.34)	8.12 (1.33)	8.96 (0.20)	8.91 (0.30)
Birthweight (gm)+ *	1830 (350)	1726 (370)	3213 (504)	2787 (538)
Birth Length (cm)	42.95 (2.20)	43.64 (5.20)	50.00 (2.73)	47.3 (2.50)
Head Circumference (cm)	29.72 (2.09)	30.25 (4.04)	33.81 (1.06)	32.69 (1.44)
Sex (% female)	44%	41%	50%	49%
At 8-weeks				
Corrected age (days)	58.65 (8.55)	56.04 (5.28)	55.08 (2.88)	57.89 (9.76)
Length (cm) *	54.93 (2.88)	53.75 (3.12)	56.13 (2.85)	53.88 (2.57)
Weight (gms)	4878 (925)	4724 (774)	4939 (770)	4898 (584)
Head Circumference (cm)	39.10 (1.92)	38.00 (1.29)	38.18 (1.76)	38.39 (1.60)
MDI (N=97)	93.57 (7.77)	93.26 (7.79)	94.96 (7.13)	90.41 (6.66)
PDI (N=94)	95.2 (11.38)	95.61 (8.78)	97.56 (10.05)	94.27 (10.04)

+Term Effect
* Drug Effect

Table 5: Significant relation between group and period of Peak Heart Rate:

Number of subjects (and percentage within the group) that exhibited their Peak HR

within each period.

Peak Period

	Preterm Drug	Preterm Control	Fullterm Drug	Fullterm Control
Attention*	13 (48%)	9 (39%)	12 (31%)	6 (21%)
Post-Motor	6 (22%)	5 (22%)	10 (26%)	4 (14%)
1-min Post	5 (18%)	5 (22%)	12 (31%)	5 (17%)
5-min Post	3 (11%)	4 (17%)	5 (13%)	14 (48%)

Note: Attention is the sum of baseline and all three attention periods due to

small expected frequencies.

Table 6: Results of Hierarchical Multiple Regressions on HR and RR arousal and arousal modulation.

	Baseline HR			Peak-Baseline HR			End-Baseline HR		
	DeltaR^2	B (SE)	Beta	DeltaR^2	B (SE)	Beta	DeltaR^2	B (SE)	Beta
Maternal Psychosocial	0.029			0.015			0.005		
Resources		1.91(1.62)	0.112		0.60 (1.67)	0.04		1.77 (2.48)	0.069
SES		2.37(2.09)	0.109		-2.73(2.15)	-0.12		-1.11(3.19)	-0.034
Quality of Care	0.019			0.002			0.002		
Instability		1.16(1.80)	0.061		-0.18(1.87)	-0.01		0.94(2.77)	0.033
Neglect		2.92(2.27)	0.128		-1.20(2.36)	-0.05		1.04(3.50)	0.03
Gestational Age	0.016			**0.056***			0.021		
Cocaine (yes/no)	0.004			**0.040***			**0.027+**		
Other drugs	0.013			0.030			0.051		
Alcohol (yes/no)		0.48(3.55)	0.017		2.00(3.51)	0.07		2.30(5.28)	0.054
Tobacco (yes/no)		2.39(3.60)	0.087		**-6.68(3.56)+**	-0.24		**-10.91(5.35)***	-0.26
Marijuana (yes/no)		-4.55(4.09)	-0.119		1.04(4.04)	0.03		9.40(6.09)	0.16

	Baseline RR			Peak RR			End RR		
	DeltaR^2	B (SE)	Beta	DeltaR^2	B (SE)	Beta	DeltaR^2	B (SE)	Beta
Maternal Psychosocial	0.025			0.004			0.001		
Resources		0.70 (1.13)	0.059		-0.54(1.13)	-0.047		0.25(1.17)	0.021
SES		-1.81(1.45)	-0.120		0.76(1.45)	0.051		0.12(1.50)	0.008
Quality of Care	0.020			0.016			0.005		
Instability		0.81 (1.59)	0.052		1.09(1.25)	0.083		-0.42(1.30)	-0.031
Neglect		1.28(1.26)	0.097		1.56(1.59)	0.099		1.05(1.65)	0.065
Gestational Age	0.000			**0.064***			**0.053***		
Cocaine (yes/no)	0.008			0.018			0.006		
Other drugs	0.014			0.047			0.022		
Alcohol (yes/no)		2.19(2.46)	0.113		**4.21(2.35)+**	0.22		0.29(2.50)	0.014
Tobacco (yes/no)		-2.24(2.50)	-0.118		**-4.15(2.38)+**	-0.22		2.69(2.54)	0.138
Marijuana (yes/no)		0.83(2.80)	0.032		0.96(2.71)	0.04		-3.87(2.89)	-0.143

Note + indicates $p<.10$; * indicates $p<.05$; and ** indicates $p<.01$
Delta R^2 is unique variance at each step, B is unstandardized partial regression coefficient (with Standard Error), and
Beta is standardized partial regression coefficient.

Captions

Figure 1: Diagram of procedure for obtaining physiological measurements of Heart Rate and Respiratory Rate.

Figure 2: Pattern of Heart Rate during protocol for drug-exposed and control 8-week-old infants.

Figure 3: Pattern of Respiratory Rate during protocol for drug-exposed and control 8-week-old infants.

Figure 4: Beginning, Peak and End Respiratory Rate for drug group and control groups of 8-week-old infants: Significant main effect of group in repeated measures ANOVA.

Figure 5: Beginning, Peak and End Respiratory Rate for preterm and fullterm infants: Significant main effect of term status in repeated measures ANOVA.

Figure 6: Beginning, Peak, and End Heart Rate by group (drug, control) and term status (fullterm, preterm): Significant three way interaction of Change in Heart Rate by group by term status.