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Prenatal Cocaine Exposure and Prematurity: Neurodevelopmental Growth

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ABSTRACT. The consequences of prematurity and prenatal cocaine exposure on early neurobehavior and physical growth were examined longitudinally in a sample of 20 cocaine-exposed and 20 non-exposed preterm neonates. The magnitude of the difference in physical growth acceleration related to prenatal cocaine exposure increased with increasing birth gestational age, whereas growth rate differences in irritability decreased. In contrast, prenatal cocaine exposure, independent of prematurity, was related to reduced attention skills at 36 weeks conceptional age and increased rates of neurobehavioral change. The effects of prenatal cocaine exposure differed with respect to the degree of prematurity, depending on the nature of the outcome examined, suggesting differing windows of vulnerability for different outcome domains. The usefulness of a developmental growth perspective was demonstrated. *J Dev Behav Pediatr 21:262–270, 2000.* Index terms: *prenatal cocaine exposure, neurobehavioral development, prematurity, growth.*

Although maternal prenatal cocaine use is associated with an increased risk of preterm delivery,[1] the majority of studies conducted to date concerning prenatal cocaine exposure have examined outcome in full-term infants. Prenatal cocaine exposure, in combination with prematurity, may confer added vulnerability for these infants,[2] compounding the developmental risk of early delivery. For example, in a recent study[3] with infants of varying birth gestational ages (30–42 weeks), cocaine-related group differences in irritability were largest for those infants born earliest in gestation. Prenatal cocaine exposure also has been associated with deficits in alertness and orientation at 36 weeks conceptional age (birth gestational age + chronological age) in preterm infants,[4] with the magnitude of the performance deficit decreasing somewhat with advancing conceptional age. Unfortunately, the longitudinal impact of the interactive effect of prenatal cocaine exposure and prematurity was not investigated in these studies.

It is possible to view the impact of prenatal cocaine exposure and prematurity in an alternative manner. Preterm delivery can be construed as a natural experiment in the timing of cessation of fetal cocaine exposure (i.e., birth is a known age point when exposure was terminated), at least until the infant is discharged from the hospital and returned to the home. Because many drug-using women use cocaine throughout pregnancy, preterm infants born earlier in gestation may incur a shorter duration of exposure than later-born preterm infants. Earlier-born cocaine-exposed preterm infants, correspondingly, may show less serious or even different developmental effects than preterm infants born later in gestation. In fact, cocaine-related physical size differences in birth weight and head size at hospital discharge were larger for infants born later in gestation.[3] Preterm opiate-exposed infants born earliest in gestation also exhibited less severe withdrawal symptoms than similarly exposed later-born preterm infants and full-term infants.[5] There are, however, significant differences in physiological effects on the developing nervous system and in the nature of withdrawal effects between opiates and cocaine. Studying the effects of prenatal cocaine exposure in preterm infants of varying birth gestational ages may shed light on the consequences of third-trimester cocaine exposure.

The organizational and growth activities of the central nervous system that occur primarily during the third trimester, and extend well into the second year of postnatal life, involve making the correct neuronal interconnections through subplate neuronal development and lamination, neurite outgrowth, and synaptic development.[6] Cocaine exposure in the third trimester, therefore, may alter synaptic connections.[7] In rats, for example, when cocaine was administered during the early postnatal period (roughly equivalent to human third trimester), the greatest changes in glucose metabolism were found in the dopamine-rich mesocortical areas[8,9] (i.e., cingulate cortex and ventral tegmental area). Third-trimester cocaine exposure also may affect these neural systems in humans.

One complicating feature in the study of prenatal exposure effects in humans is maternal polydrug use during pregnancy. In a previous study with this sample,[4] cocaine-related deficits in neonatal motor development were no longer

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significant when the effect of prenatal alcohol exposure was controlled statistically. However, differences in attention skill were robust when such differences were controlled. In contrast, other studies[3] have not found that comorbid prenatal alcohol exposure contributed significant variability to outcome in preterm cocaine-exposed infants. Because various substances differ in their effects on the developing brain, it is important to consider carefully the issue of maternal polydrug use during pregnancy.

Findings from experimental studies with monkeys[10] indicate that behavioral alterations resulting from a neurochemical brain insult depend on the developmental sequence by which various brain areas subsume different cognitive functions with maturation. Maturational effects can be quantified statistically by the use of developmental growth curve trajectories, in which developmental outcome is plotted as a function of age. The resulting maturational growth curves can be described statistically by several parameters, such as the performance level at a given age and linear or quadratic rates of change in performance across age. It is possible to isolate the effects of an independent predictor, such as prenatal cocaine exposure or prematurity, on these growth parameters.[11–13] Prenatal cocaine exposure and prematurity may affect developmental growth parameters differentially, thereby describing how prenatal exposure alters the developmental process. The purpose of this study was to determine whether the developmental effects of prenatal cocaine exposure varied as a function of prematurity at birth.

METHODS

Subjects

Consecutively admitted, cocaine-using women who delivered preterm (28–37 weeks gestation) infants were recruited prospectively within 24 hours of birth from an urban, public hospital. Infants of birth gestational ages ≥ 28 weeks were recruited to limit participation to infants at low risk for major neurosensory handicap.[14] Therefore, infants with the following conditions known to be related to poorer developmental outcome were excluded: specific genetic syndromes or major malformations, seizure, hydrocephalus, perinatal asphyxia, HIV, major infection, cerebral hemorrhage greater than Grade I, periventricular leukomalacia, brochopulmonary dysplasia, and necrotizing enterocolitis. One woman refused study participation, leaving a final sample of 20 preterm cocaine-exposed (CE) infants (n = 3 infants ≤ 32 wks, n = 8 infants 33–35 wks, and n = 9 infants 36–37 wks). After a CE infant was enrolled, the next woman who delivered a preterm infant matching the CE infant in sex, race, and birth gestational age, but who did not use cocaine during pregnancy, was recruited. All non-cocaine-using women who were approached consented, with 20 non-exposed (NE) infants participating. Sample characteristics are listed in Table 1. There were no differences between groups except in maternal age. Consistent with results from other studies,[3] women in this sample who used cocaine during pregnancy were older than those who did not. Thirteen CE infants received some type of oxygen therapy during hospitalization (n = 8 ventilated), whereas 15 NE infants received oxygen therapy (n = 4 ventilated). There was no difference in the number of infants who were ventilated between exposure groups ($\chi^2[1, n = 40] = 1.90, p > .17$). One of the CE infants had a Grade I hemorrhage that resolved before evaluation. One CE infant was small for gestational age. A similar number of infants in each group (n = 9 CE; n = 8 NE) received phototherapy for hyperbilirubinemia.

Table 1. Demographic and Drug Exposure Characteristics of Cocaine-Exposed and Non-exposed Preterm Infants

	CE (n = 20)		NE (n = 20)	
Variable	Mean	SD	Mean	SD
Birth gestational age (wk)	34.35	2.66	34.35	2.72
Birth weight (kg)	2.12	0.62	2.32	0.66
Birth head circumference (cm)	30.40	2.41	31.60	1.96
Hospital days	16.75	16.35	11.90	13.61
Ventilation days[a]	6.25	3.11	5.50	3.00
Maternal age*	29.60	6.34	21.70	4.94
Maternal education	11.45	1.36	11.10	1.74
Tobacco use during pregnancy[b]	11.37	8.49	6.52	2.36
Alcohol use during pregnancy[c]	0.10	0.09	0.08	0.07
Frequency of cocaine use[d]	0.99	0.96	—	—

CE, cocaine-exposed; NE, non-exposed; SD, standard deviation.
From Espy et al[4]; frequency of cocaine use, ventilation days added.
[a]For ventilated infants only (n = 8, CE; n = 4, NE).
[b]Mean cigarettes per day during the entire pregnancy for consumers only (n = 12, CE; n = 3, NE).
[c]Mean alcohol consumption per day during the entire pregnancy for consumers only (n = 17, CE; n = 5, NE), reported in terms of absolute alcohol ounces per day.[15]
[d]Number of episodes of cocaine consumption reported per week.
*$p < .01$.

Drug Use. Within 24 hours of delivery, a confidential interview to determine the quantity-frequency-variability parameters for each substance used prenatally was conducted by the first author in a structured format relative to pregnancy landmarks.[16] Additional information was obtained from the medical records as needed. This information was summed and averaged to yield substance use indices across the entire pregnancy. CE infants were defined as those with (1) a positive drug screen for cocaine or its metabolites in meconium and/or urine samples taken from the mother or infant, and/or (2) admitted maternal use without a positive drug test result. The most frequent means of using cocaine was by smoking (45%), with a frequency of greater than once per week (45%) through the entire pregnancy (85%). To be included in the NE group, mothers were required to deny illicit drug use during pregnancy and to consent to having their infants tested for substance exposure by meconium and/or urine sampling.

The infants' meconium and/or urine was collected and submitted to the laboratory to be analyzed for the presence of cocaine, marijuana, and opiates. Meconium or urine analysis results were obtained for all CE infants and for seven of the NE infants. Results of meconium screenings of all seven NE infants were negative. Meconium samples from four NE infants were composed of transitional stool and, therefore, were not useful. The laboratory lost the remaining nine meconium samples from NE infants. Because the women who consented to

meconium testing were informed fully of the nature and sensitivity of these analyses before consenting, it is assumed that the women would not risk detection of prenatal substance use if they had used drugs during pregnancy and denied such use on interview. Moreover, only 3.4% of women delivering in this hospital (with some overlap of recruiting periods) used cocaine, with no difference obtained between maternal self-report and meconium sampling methods.[17] It was considered to be a reasonable assumption that the NE cohort was, in fact, free from illicit drug exposure. If this assumption were not valid, the effect would be to erroneously assign a CE infant to the NE group, rendering the groups more similar. In this case, the statistical analyses would be more conservative, that is, less likely to find true group differences.

Prenatal alcohol and tobacco use information also is presented in Table 1. The average amount of maternal alcohol and tobacco consumption was low and did not differ between the CE and NE groups. Consistent with other reports of cocaine-using women, however, the number of women who used alcohol or tobacco during pregnancy differed by infant group: alcohol, $\chi^2(1, n = 40) = 8.64, p < .01$; tobacco, $\chi^2(1, n = 40) = 14.56, p < .01$. Twelve cocaine-using women and 3 non-using women used alcohol during pregnancy, and 17 cocaine-using women and 5 non-using women used tobacco during pregnancy. Use of illicit drugs other than cocaine occurred too infrequently to be analyzed statistically. Five cocaine-using women reported marijuana use during pregnancy. Barbiturate use was reported by 4 women, codeine and heroin use was reported by 2 women, and Valium and Talwin use was reported by 1 woman. Four women used only cocaine during pregnancy.

Measures

Predictors. Prenatal cocaine exposure, prematurity, and the respective interaction were the predictors of interest. Prenatal cocaine exposure was dummy-coded (1 = CE, 0 = NE). Quantity estimations of cocaine exposure were not reliable because of (1) the difficulty that these women had in estimating the amount of cocaine used (leading to missing data for many women), (2) the unknown variability in the purity of cocaine in the purchased product, and (3) the differential routes of drug administration among women. Therefore, quantity estimations were not analyzed here.

Prematurity was coded as the number of weeks that birth occurred before the estimated due date, which was determined from information available in infant and maternal medical charts. Consistent with findings from other studies with neonates, the same medical chart information was not available for all participants. For the purposes of this study, the following information was used, in order[18]: (1) the date of last menstrual period; (2) estimated due date from an ultrasound scan conducted before 20 weeks gestation; and (3) Ballard scores.[19] Ballard scores were not used in isolation because of inaccuracy with low birth weight infants,[20,21] possibly introducing nonrandom error into the gestational age estimate.

Outcome. Two domains were measured: neurobehavior and physical growth. The Neurobehavioral Assessment of the Preterm Infant (NAPI)[22] was used to measure early neurobehavior, because it was developed specifically to monitor maturational change in hospitalized preterm infants.[23] The NAPI can be administered when the infant is healthy enough to be handled, and it has been validated for use through 37 weeks conceptional age.[22] To maximize reliability, only those scales with more than one item were considered for analysis. The NAPI Alertness and Orientation (AO) scale was included because of its sensitivity to prenatal cocaine exposure-related differences in preterm infants[4] and full-term infants in like domains on other neurobehavioral measures.[3,24] The AO scale contains items concerning the quality of alertness and responsivity to visual and/or auditory stimulation. Unlike AO, Irritability (IR)[4] and Motor Development and Vigor[3,4] scales have not been robustly related to prenatal cocaine exposure. In previous studies, prenatal cocaine exposure was either unrelated to performance on the Motor Development and Vigor scale,[3] or was no longer significant when prenatal alcohol exposure was controlled statistically.[4] To reduce the likelihood of spurious cocaine-related findings, this scale was not used as a dependent measure. Although there were no effects of prenatal cocaine exposure on IR development in a previous study with this sample,[4] it was included here because the effect of prenatal cocaine exposure had differed as a function of birth gestational age in another study.[3] IR items concern the extent of crying during evaluation. Both AO and IR scores increase with conceptional age,[22] as preterm infants become more alert, reactive, and irritable with maturation. Two neonatal physical growth measurements, head circumference (HC) and body weight (BW), were taken from infant medical charts. Numerous previous studies with full-term infants have demonstrated cocaine-related effects on both HC and BW at birth, in isolation and when controlling for other prenatal substance exposure, although findings from investigations with preterm infants are equivocal.[3]

Maternal prenatal alcohol and tobacco use were not controlled statistically in these analyses because of the small sample size. To maintain adequate power to detect significant effects, the small sample size limited the number of predictors that could be included in a given model. The dependent variables were chosen carefully, including only those in which results from previous studies indicated unique cocaine exposure effects, because the focus of this article was to determine whether documented cocaine effects in preterm infants varied as a function of prematurity. Interested readers are referred to a previous article with this sample focusing on the relative contribution of prenatal exposure to cocaine, alcohol, and tobacco on developmental growth.[4] When the amounts of prenatal alcohol use (average ounces of absolute alcohol [AA] per day consumed during entire pregnancy) and tobacco use (average number of cigarettes per day consumed during entire pregnancy) were included in the models, all results were comparable (i.e., the magnitude of the cocaine effect was similar and remained significant after statistical control) with the exception of the AO cluster, in which prenatal cocaine exposure only marginally predicted the linear change rate ($p < .10$). These unpublished results are available from the first author upon request.

Procedure

The NAPI was administered by the first author (K.A.E.), who had received training and certification in administration and scoring from Dr. Korner and her staff. It was not

possible for the examiner to be blinded to the infants' exposure status. Unlike full-term infants who can be removed from the nursery for blind evaluation to prevent tester contact with parents, nursing staff, and charts that provide information concerning exposure status, [24] preterm infants are required to be in close proximity to medical equipment and hospital staff in the Neonatal Intensive Care Unit, particularly early in the hospital course. Periodic reliability checks were conducted with the third author (M.L.R.) who was blinded to the exposure status of the infant. No differences of greater than a half point were obtained between raters.

The NAPI was administered in the hospital nursery while the infant was in an isolette or in an open crib under a warmer. NAPI evaluations were conducted approximately 1 hour before scheduled feeding to decrease the influence of behavioral state on test performance. Infant assessments were attempted daily during hospitalization, as the medical condition permitted. This schedule allowed for the collection of multiple data points per subject, providing a robust estimation of neurobehavioral change during the developmental period of greatest instability.[27] Because the NAPI involves handling and removing the infant from the heat source for a brief period of time, infants could not be tested if connected to a respirator or intravenous lines. To minimize stress to earlier-born infants, these infants were assessed every 2 to 3 days early during hospitalization, according to nursery staff requests. Infants were not tested on a given day if they had undergone any stressful medical procedure that day. The first assessment was conducted at least 24 hours after birth. Male infants were evaluated at least 24 hours after circumcision.

HC and BW measurements were taken at least once per day by trained neonatal medical staff, regardless of infant health. When infants were ill, as many as six physical measurements were taken in a day. For the purposes of analysis, all measurements taken during a day were averaged to form a single, daily composite. Charted growth measurements were used, rather than those taken directly by the examiner at the time of neurobehavioral evaluation, to allow more data points per infant, leading to a more precise statistical modeling of the actual developmental growth trajectory. Although these measurements were taken by different trained medical staff and direct reliability estimates were unavailable, the measurements generally increased progressively, with modal differences between adjacent measurements of 0.0 cm for HC and .020 kg for BW.

Evaluation information is presented in Table 2. To reduce examiner-related performance differences, a single examiner conducted a total of 173 NAPI evaluations.[27,28] Infants were evaluated an average of 4.2 times, with no group differences in the mean number of NAPI evaluations or in the mean conceptional age at the initial or final NAPI evaluation. Infants received an average of 13.7 head measurements and 14.1 weight measurements. The mean number of HC and BW measurements was comparable between CE and NE groups, as were conceptional ages at the initial and final physical measurement occasions.

Table 2. Evaluation and Measurement Characteristics of Cocaine-Exposed and Non-exposed Preterm Infants

	CE (n = 20)		NE (n = 20)	
Variable	Mean	SD	Mean	SD
No. of NAPI evaluations	4.8	3.3	3.8	2.5
Initial NAPI conceptional age (wk)	35.5	1.7	35.1	2.1
Final NAPI conceptional age (wk)	36.4	1.3	35.9	1.7
No. of HC measurements	15.4	14.8	11.9	12.9
No. of BW measurements	16.0	15.3	12.3	13.4
Initial physical measurement conceptional age (wk)	34.3	2.7	34.3	2.7
Final physical measurement conceptional age (wk)	36.4	1.3	35.9	1.7

CE, cocaine-exposed; NE, non-exposed; NAPI, Neurobehavioral Assessment of the Preterm Infant[23]; SD, standard deviation; HC, head circumference (cm); BW, body weight (kg).

Analysis

Growth curve analysis was used to analyze the longitudinal data. These analyses can be considered conceptually to consist of two phases, an individual (within-subject) phase and a group (between-subject) phase, although both phases actually are conducted simultaneously. To estimate the within-subject model parameters, individual growth curves were calculated by regressing the respective outcome (AO, IR, HC, or BW) variable on conceptional age. Growth curve parameters can include, for example, intercept, linear, and quadratic terms, where the number of terms is constrained by the number of data points available.

Developmental hypotheses were examined using a mixed-model approach with restricted maximum likelihood estimation. PROC MIXED from the SAS®, version 6.12, was used. For the statistical analysis, two sets of models were fit: (1) unconditional models that examined the mean and variance of the within-subjects parameters, and (2) conditional models that accounted for the variance in within-subject parameters. All models were fit for each outcome variable separately. The unconditional models included (1) an intercept, representing an infant's expected AO, IR, HC, or BW at 36 weeks conceptional age, and (2) a linear slope parameter, quantifying the change in pertinent outcome per week of conceptional age. For HC and BW, a quadratic term also was included. This term described the extent to which the slope of the line tangent to the growth curve trajectory at 36 weeks conceptional age increased (i.e., was positive) or decreased (i.e., was negative). The form of the within-subject model was determined by (1) visually examining the shape of the individual and group growth trajectories, (2) statistically testing for significant variance in growth (Wald test), and (3) contrasting fit indices of competing models (−2 Log likelihood, Akaike's Information Criteria, and Schwarz's Bayesian Criteria).[27] From these individual curves and corresponding parameter estimates, aggregate group curves were derived and expressed in terms of between-subject variables. These conditional models were fit to examine the influence of the predictor variables on the growth parameters, entering prenatal cocaine exposure, prematurity, and the respective interaction in a single block.

Intercept values and their variance depend on the conceptional age, which has been set arbitrarily equal to zero in the

model, referred to as the centering point for age. When a quadratic term is included in the model, the linear slope parameter and its variance also depend on centering choice. Centering the data allows questions concerning inter-individual differences in growth to be addressed by "cutting" the growth curve at a particular age of interest. There is considerable flexibility in the choice of a centering point, as it is accomplished by transforming the variable scale to meaningful units through simple subtraction. If the analyses are not centered, implausible parameter estimates may result. For example, the AO intercept value represents AO skill when infant conceptional age is truly zero in the uncentered model, that is, at conception. In the analyses reported here, age was centered at 36 weeks conceptional age because it was inside the range of the data for most infants and represented the age around which most preterm infants were discharged from the hospital.

RESULTS

Unconditional Models: Examination of Within-Subject Parameters

Physical Growth. All mean growth parameters differed from zero, indicating that head circumference (HC) changed with age. Although studies typically find nonlinear physical growth patterns in children,[28] those investigations were conducted over much longer time periods (years vs days, as in this study). Given the much shorter time frame of this study, it is not surprising that linear models adequately captured change in physical growth. In Table 3, expected HC and linear growth in HC was 32.0 cm and 0.8 cm per conceptional week at 36 weeks conceptional age, whereas quadratic growth in HC was estimated as 0.1 cm per conceptional week-squared. HC and linear growth in HC variance differed from zero, whereas variability in quadratic growth in HC did not. Therefore, HC and linear growth in HC differed among individual infants, but quadratic growth in HC was comparable.

Table 3. Results of the Unconditional Model

Outcome Measure	Mean	SE	Estimated Parameter Variance
Physical growth			
HC intercept	32.0***	0.26	2.47***
HC slope	0.8***	0.08	0.13**
HC acceleration[a]	0.1***	0.01	–
BW intercept	2.396***	0.081	0.253***
BW slope	0.004	0.036	0.041**
BW acceleration[a]	0.019***	0.001	–
Neurobehavioral growth			
AO intercept	48.0**	2.54	144.33*
AO slope[a]	0.8	1.22	–
IR intercept	47.5**	3.30	270.34**
IR slope[a]	6.8**	1.51	–

Intercept parameter is the average level at 36 weeks conceptional age. AO and IR are the Alertness and Orientation and Irritability clusters from the Neurobehavioral Assessment of the Preterm Infant,[23] respectively. HC, head circumference (cm); BW, body weight (kg); SE, standard error.

[a]Parameter variance was fixed because of a lack of significant variability across subjects.

*$p < .05$; **$p < .01$, ***$p < .001$.

At 36 weeks conceptional age, average infant body weight (BW) was estimated as 2.396 kg. Linear growth in BW at 36 weeks conceptional age did not differ from zero, whereas mean quadratic growth in BW of .019 kg per conceptional week-squared did. As with HC, variance in estimated BW and linear growth in BW differed from zero, but quadratic growth in BW did not. The power to detect individual variability is affected by both the number of infants and time points. The estimation of individually varying quadratic growth may have been limited by the relatively short time series for some infants.

Neurobehavior. Estimated performance on the Attention and Orientation (AO) scale at 36 weeks conceptional age was 48.0 points, whereas linear growth was 0.8 points per conceptional week. Variance in the intercept differed from zero, but variance in linear growth did not. Therefore, AO skill at 36 weeks conceptional age was infant-specific, but AO growth was constant across the age range studied here. There was substantial day-to-day variability in AO cluster scores with no consistent developmental trend, which reflected the infants' highly variable state across daily evaluations.[25] For the Irritability (IR) scale, preterm infants were estimated to score 47.5 cluster points, on average, at 36 weeks conceptional age. Developmentally, IR scores were expected to increase positively. Crying and general fussiness become more prevalent with age and can be viewed as markers of increasing maturity.[29] Indeed, linear rates of change in IR differed from zero in the positive direction ($\gamma = 6.8$ cluster points per conceptional week). Like AO, there was significant variance in IR intercept parameters, but not in linear growth. Interested readers also are referred to Espy et al[4] for a further description of the modeling procedure used for AO and IR.

Conditional Models: Correlates of Within-Subject Parameters

The effects of prenatal cocaine exposure, prematurity, and their interaction are depicted in Tables 4 and 5. As hypothesized, the interaction of cocaine exposure and prematurity significantly predicted the specific growth parameters for HC, BW, and IR measures. Contrary to prediction, the effects of prenatal cocaine exposure on AO development did not vary as a function of prematurity.

Head Circumference. The interactive effect of prenatal cocaine exposure and prematurity predicted quadratic growth in HC (Table 4), but not the HC intercept and linear growth parameters. There also were significant main effects of prenatal cocaine exposure on the HC intercept and quadratic growth parameters and main effects of prematurity on both linear and quadratic growth parameters. These effects are depicted most easily by calculating (1) the derived equations that describe growth for cocaine-exposed (CE) and nonexposed (NE) infants, and (2) the corresponding predicted quadratic growth values from these equations. This information is presented in Tables 6 and 7, respectively.

In Table 6, the intercept, that is, the expected outcome value at 36 weeks conceptional age, is the first term in the equation. For example, the HC of a typical CE infant at 36 weeks conceptional age was 31.2 cm. The next term is an adjustment that is made to the intercept to take into account how prematurely the infant was born. When the value of the

Table 4. Results of the Conditional Model—Physical Growth

	HC		BW	
	γ	SE	γ	SE
Intercept parameter[a] effects				
Intercept	32.4***	0.41	2.790***	0.139
Cocaine	−1.2**	0.47	−0.295*	0.139
Prematurity	0.1	0.09	−0.085***	0.027
Linear growth parameter[a] effects				
Linear	0.4**	0.14	−0.161***	0.048
Cocaine	−0.2	0.12	−0.041	0.049
Prematurity	0.1***	0.02	0.067***	0.009
Quadratic growth parameter effects				
Quadratic	0.17***	0.04	0.068***	0.007
Cocaine	−0.11*	0.05	−0.041***	0.008
Prematurity	−0.01*	0.01	−0.006***	0.001
Cocaine × prematurity	0.01*	0.01	0.005***	0.001

γ is the mean value of the parameter estimate, where intercept and linear parameters are the respective average size and linear change rate at 36 weeks conceptional age. HC, head circumference (cm); BW, body weight (kg); SE, standard error.

[a]The "Cocaine × Prematurity" term was nonsignificant and deleted from the model to estimate the main effects more precisely.

*$p < .05$; **$p < .01$; ***$p < .001$.

Table 5. Results of the Conditional Model—Neurobehavior

	AO		IR	
	γ	SE	γ	SE
Effects on intercept parameter[a]				
Intercept	45.0**	3.71	55.4***	5.54
Cocaine	−9.6*	3.88	6.0	6.37
Prematurity	3.3**	0.93	−3.1*	1.38
Effects on linear growth parameter				
Linear	−0.6	2.67	2.4	4.64
Cocaine	5.8**	2.08	−6.3	5.93
Prematurity	0.5	0.33	−0.1	0.61
Cocaine × prematurity[a]	–	–	2.5*	1.02

γ is the mean value of the parameter estimate, where the intercept and linear parameters are the respective performance level and change rate at 36 weeks conceptional age. AO and IR are Alertness and Orientation and Irritability clusters from the Neurobehavioral Assessment of the Preterm Infant,[23] respectively. SE, standard error.

[a]The "Cocaine × Prematurity" term was nonsignificant and deleted from the model to estimate the main effects more precisely.

*$p < .05$, **$p < .01$; ***$p < .001$.

Table 6. Equations Describing Change for Cocaine-Exposed and Non-exposed Infants

Physical growth

Head circumference

$HC_{CE} = 31.2 + (0.1 \times P) + (0.3 \times Age) + (0.1 \times [P \times Age]) + (0.06 \times Age^2)$

$HC_{NE} = 32.4 + (0.1 \times P) + (0.4 \times Age) + (0.1 \times [P \times Age]) + (0.17 \times Age^2) + (-0.01 \times [P \times Age^2])$

Body weight acceleration

$BW_{CE} = 2.495 + (-0.085 \times P) + (-0.120 \times Age) + (0.067 \times [P \times Age]) + (0.027 \times Age^2) + (-0.001 \times [P \times Age^2])$

$BW_{NE} = 2.790 + (-0.085 \times P) + (-0.161 \times Age) + (0.067 \times [P \times Age]) + (0.068 \times Age^2) + (-0.006 \times [P \times Age^2])$

Neurobehavioral growth

Alertness and Orientation

$AO_{CE} = 35.4 + (3.3 \times P) + (5.2 \times Age) + (0.5 \times [P \times Age])$

$AO_{NE} = 45.0 + (3.3 \times P) + (-0.6 \times Age) + (0.5 \times [P \times Age])$

Irritability

$IR_{CE} = 61.3 + (-3.1 \times P) + (-3.9 \times Age) + (2.4 \times [P \times Age])$

$IR_{NE} = 55.4 + (-3.1 \times P) + (2.4 \times Age) + (0.5 \times [P \times Age])$

AO and IR are Alertness and Orientation and Irritability clusters from the Neurobehavioral Assessment of the Preterm Infant,[23] respectively. These equations are calculated using the growth parameter estimates provided in Tables 4 and 5. P, prematurity; Age, linear slope; P × Age, linear slope adjustment for prematurity; Age^2, acceleration; [P × Age^2], acceleration adjustment for prematurity; CE, cocaine-exposed; NE, non-exposed; HC, head circumference (cm); BW, body weight (kg).

Table 7. Change Parameter Values by Birth Gestational Age

	Birth Gestational Age (wk)		
	32	34	36
Physical growth			
Head circumference acceleration[a] (cm^2)			
Cocaine-exposed	0.13	0.13	0.13
Non-exposed	0.22	0.27	0.32
Body weight acceleration[a] (kg^2)			
Cocaine-exposed	0.044	0.048	0.052
Non-exposed	0.076	0.100	0.124
Neurobehavioral growth			
Alertness and orientation slope			
Cocaine-exposed	8.8	7.9	7.0
Non-exposed	2.9	2.0	1.2
Irritability slope			
Cocaine-exposed	8.0	3.2	−1.5
Non-exposed	2.0	2.1	2.3

These values are calculated from equations using the parameter effects depicted in Table 5 as variable coefficients.
[a]Acceleration is calculated[30] from the first derivative of the quadratic term ($\gamma \times^2$) = $2\gamma X$.

prematurity adjustment constant is the same across CE and NE groups, it means that the prematurity effect did not differ by cocaine exposure status. The next two terms in the equation are the expected linear growth rate and the adjustment to that linear rate for prematurity, respectively, with the final two terms representing the quadratic growth rate (acceleration) and the associated prematurity adjustment. For the HC equations, there is no prematurity adjustment term for quadratic growth for the CE group because the value was 0. As shown in Table 6, it is apparent that HC is smaller for CE infants at 36 weeks gestational age (CE = 31.2 cm; NE = 32.4 cm). The rate of linear growth in HC also was reduced in CE infants (0.3 cm per conceptional week) compared with NE infants (0.4 cm per conceptional week), as was HC acceleration (CE = .06 cm per conceptional week-squared; NE = .17 cm per conceptional week-squared).

In Table 7, the interactive effects of prenatal cocaine exposure and prematurity on acceleration are depicted by presenting the actual parameter growth values, calculated by substituting the relevant information into the equations from Table 6. HC acceleration was 0.13 cm^2 for CE infants, independent of prematurity, whereas for NE infants, HC acceleration was most rapid for those born latest in gestation. Across birth gestational ages, HC growth acceleration was larger in NE infants, with the magnitude of the group difference increasing with greater birth gestational age. Therefore, as preterm infants age, the net or cumulative effect of the reduced linear growth and acceleration in CE infants results in smaller HC at 36 weeks conceptional age compared with NE infants.

Body Weight. In Table 5, the interactive effect of prematurity and prenatal cocaine exposure predicted quadratic growth in BW, but not the linear growth or intercept parameters. There also were main effects of prenatal cocaine exposure on the BW acceleration and intercept parameters and of prematurity on all three BW growth parameters. As seen in Table 6, CE infants weighed less at birth than NE controls at 36 weeks conceptional age. The rate of linear growth in BW was attenuated (i.e., less negative) in CE infants, and positive acceleration in BW was reduced in CE infants. In both groups, prematurity attenuated BW acceleration, to a larger degree for NE infants. In Table 7, for CE infants, BW acceleration increased minimally with birth gestational age (i.e., 0.044 kg^2–0.052 kg^2), whereas BW accelerated more rapidly in NE infants. The magnitude of the difference in BW acceleration between CE and NE infants also increased progressively with birth gestational age. Like HC, the cumulative negative effect of prenatal cocaine exposure on the linear and quadratic growth parameters was manifested as reduced BW at 36 weeks conceptional age.

Irritability. Linear IR growth was predicted by the interaction of cocaine exposure and prematurity. In Table 6, for CE infants, increasing prematurity mitigated the negative growth rate, whereas for NE infants, prematurity augmented the positive base growth rate. In Table 7, it is apparent that among infants born earlier in gestation, the difference in linear IR growth between CE and NE infants was largest in those born earliest in gestation, with IR scores changing more rapidly in CE infants. Interestingly, in infants born at 36 weeks gestational age, linear IR growth decreased only in CE infants. Because infants born close to term had a shorter evaluation time series because of shorter hospital stays, declining IR growth among CE infants may reflect acute systemic effects of residual cocaine. Prematurity independently predicted the IR score at 36 weeks conceptional age. Infants born earlier in gestation were less irritable at 36 weeks conceptional age than later-born infants.

Attention. The interaction of prematurity and prenatal cocaine exposure did not predict the level of linear growth in AO. In Table 5, AO at 36 weeks conceptional age was adversely affected by prenatal cocaine exposure, but CE infants gained, on average, 5.8 more AO points per conceptional week than NE controls. These cocaine-related differences, however, did not vary by prematurity. These results are apparent in Table 7 showing the difference in linear growth in AO to be constant between CE and NE infants. On the other hand, prematurity was associated with higher AO cluster scores at 36 weeks conceptional age (in Table 5, $\gamma = 3.3$ points per week of gestational age), which is consistent with the findings of others[23] that AO scores are affected more by postnatal experience than by gestational age.

DISCUSSION

The effect of prenatal cocaine exposure on change in head circumference, body weight, and irritability depended on how prematurely birth occurred. Greater reductions in physical growth acceleration were observed between cocaine-exposed (CE) and non-exposed (NE) preterm infants who were born at later gestational ages. The smaller head size and lower birth weight in CE infants at 36 weeks conceptional age reflected the cocaine-related dampening of the growth trajectory. These longitudinal results are consistent with those of Brown et al[3] who used a cross-sectional design. The present study demonstrates a specific developmental mechanism for the physical size differences, namely differential growth acceleration. These results also are consistent generally with the observation of

less severe physical withdrawal symptoms in preterm opiate-exposed neonates born earliest in gestation.[5] Because opiates and cocaine differ in neurophysiological and withdrawal effects, these concordant findings may validate the moderating influence of prematurity on prenatal cocaine exposure.

For early irritability, differences among CE and NE infants in linear growth were largest for those infants born earliest in gestation, with CE infants exhibiting faster rates of change in irritability. Brown and colleagues[3] also found that cocaine-related differences in irritability were largest for infants born earliest in gestation, although irritability was assessed at hospital discharge rather than longitudinally. Results from the current investigation are consistent with those findings but suggest, additionally, that the developmental course for irritability differed among CE and NE infants. Early-born CE infants were less irritable perinatally, but growth in irritability was more rapid. At 36 weeks conceptional age, CE infants were more irritable than like-aged NE infants, which was consistent with other[3] findings.

It may be that greater rates of change in irritability for CE infants resulted from a scaling artifact, in which points are gained more easily when performance is at the lower end of the scale. Furthermore, the sample size was small, with relatively few babies sampled at the earlier birth gestational ages. Such a design may render the developmental parameter estimates less stable for younger preterm infants. Post hoc power estimates, using a repeated-measures design, ranged from .71 to .76. One advantage of the multilevel approach to growth curve analysis, however, is the differential weighting of subjects, whereby those with more precise data (i.e., more data points across a wider age range) receive greater weight in determining the mean growth trajectory.[30] Thus, the earlier-born infants were evaluated on more occasions across conceptional age, increasing the estimation precision.

In contrast to irritability, the effect of prenatal cocaine exposure on attention development was independent of prematurity. Regardless of when in gestation birth occurred, prenatal cocaine exposure was associated with lower attention performance and increased linear rates of change. These null results agree with those of Brown et al,[3] but differ from those of Scafidi et al,[31] in which CE preterm infants demonstrated heightened stimulus attention. These discordant findings may be related to when neurobehavior was evaluated. In the latter study, testing was conducted at varying conceptional ages across subjects (mean = 34 wks). In this study, longitudinal data were collected at multiple time points.

In conjunction with our previous results,[4] these findings suggest that cocaine-related effects in preterm infants are not a consequence of prematurity exclusively. Contrary to previous suggestion,[32] prematurity did not subsume or indirectly mediate, but rather moderated, the effects of prenatal cocaine exposure. Premature birth in some sense may be "protective" for CE infants whose mothers used cocaine until delivery, because the fetus is exposed for a shorter duration. That is, early delivery relieves the fetus from further cocaine exposure. Premature birth, of course, cannot be viewed as "positive" per se because of the relatively high risk of medical complications and adverse outcome.[14] Even in this study, cocaine-related effects on irritability were more deleterious in earlier-born preterm CE infants.

Additionally, those functional systems that are developing rapidly during the third trimester may be most vulnerable to disruption.[33] Physical growth progresses rapidly during this period, with steadily larger incremental changes in fetal physical size as term approaches. Exposure to cocaine late in the third trimester, then, would impair growth to a greater degree than like exposure earlier in the third trimester. Using prematurity as a marker for cessation of exposure allows for the future investigation of the differing windows of vulnerability for different neurobehavioral domains.

The significant effects were observed during a relatively short developmental period, proximal to birth. One advantage of examining outcome during neonatal hospitalization is that new postnatal substance exposure is removed. One relative disadvantage of this design is that it is possible that some of the exposure agent may have remained in the infant's system, although cocaine is metabolized relatively rapidly.[34] Behavioral testing was not initiated until the infant was medically stable. Stability was achieved within a few days to a few weeks after birth, depending in part on birth gestational age. Potential residual concentrations of cocaine, therefore, may account for the declining change in irritability in CE infants born at 36 weeks gestation. In contrast, physical measurements were taken from birth until hospital discharge. Therefore, the residual drug concentration might have affected early measurements. One advantage of growth curve analysis, however, is that the importance of any given measurement is minimized relative to others in the growth trajectory.[30]

Although the multilevel approach to longitudinal data used in this study is a strength, one consequence of the small sample size was the limit on the number of influences able to be examined simultaneously in a given model. Because of power limitations, the effects of prematurity could not be examined in light of the effects of prenatal exposure to other substances. Although analyses were limited to those outcomes where cocaine-related effects were robust when other substance exposures were controlled statistically,[3,4] the effect of prematurity may have differed if these other exposures had been controlled or experimentally manipulated. Future longitudinal studies with larger samples of preterm infants should consider using the multilevel approach to address this question.

Another limitation is the lack of blind neurobehavioral assessments. Given the overlap in evaluation of NE and CE infants hospitalized concurrently, it is not likely that examiner expectations had a significant effect on neurobehavioral outcome scores.

Despite these caveats, our findings demonstrate that the effects of prenatal cocaine exposure on early neurodevelopment are related to prematurity and that the nature of the effect depended on outcome domain. Prematurity may serve as a proxy for the duration or timing of third-trimester exposure, which may be important in determining early development. An important goal of future studies is to disentangle the outcome effects of the amount and duration of prenatal exposure. Longitudinal follow-up after hospital discharge also would be beneficial to determine whether these interaction effects persist.

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