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Neurobehavior in Preterm Neonates Exposed to Cocaine, Alcohol, and Tobacco

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Neonatal neurobehavioral development was investigated in a sample of 20 hospitalized, prenatally cocaine-exposed preterm infants and 20 matched non-exposed controls. Prenatal cocaine exposure was related to reductions in attention performance that remained apparent at 36 weeks conceptional age. There was no impact of prenatal cocaine exposure on the rate of change in attention proficiency. In utero alcohol exposure was associated with increased rates of age-related change in motor skill. Alcohol-related performance deficits were transient; alcohol-exposed infants reached an equivalent level of motor performance exhibited by the non-exposed infants by 36 weeks conceptional age. These findings highlight the importance of considering potential effects of prenatal cocaine exposure in the context of other substance exposure and demonstrate the utility of a developmental perspective to address the impact of prenatal substance exposure on outcome.

prenatal cocaine exposure prenatal alcohol exposure prematurity
neurobehavioral development neonatal growth curve analysis

Fullterm infants prenatally exposed to cocaine initially were portrayed as exhibiting marked deficits during the neonatal period in state regulation, motor control, and stimulus orientation and alertness (Chasnoff, Burns, Schnoll, & Burns, 1985). Other investigations, utilizing better controlled prospective designs, have not reported the severity and consistency of neurobehavioral disturbance (e.g., Coles, Platzman, Smith, James, & Falek, 1992; Eisen et al., 1991; Mayes, Granger, Frank, Shottenfeld, & Bornstein, 1993; Neuspiel, Hamel, Hochberg, Greene, & Campbell, 1991; Woods, Eyler, Behnke, & Conlon, 1993). These studies share three limitations. First, sample participation was limited to healthy full-term infants because neurobehavioral status was assessed with the Brazelton Neurobehavioral Assessment Scale (Brazelton, 1984). Prenatal cocaine use, however, has been associated consistently with increased risk of preterm delivery (Gillogley, Evans, Hansen, Samuels, & Batra, 1990). In one study, for example, almost 30% of the polydrug-exposed infants were excluded from participation because of preterm birth (Chasnoff, Griffith, MacGregor, Dirkes, & Burns, 1989). Because preterm infants have a well-documented, pre-existing risk for subsequent developmental delay (Caputo & Mandell, 1970), elimination of preterm infants may yield an overly optimistic view of the effects of cocaine exposure.

Second, performance on neurobehavioral evaluations conducted after hospital discharge is affected by multi-factorial issues which complicate the detection of the direct biochemical effects of prenatal cocaine exposure (Mayes & Bornstein, 1995). Even at 1 month of age, neurobehavioral status may be influenced, in part, by other indirect factors that are related to maternal substance abuse but which are not direct biochemical consequences of the prenatal exposure, such as impaired maternal interactive style (Brinker, Baxter, & Butler, 1994; Woods et al., 1993). In addition to prenatal cocaine exposure, the comorbid effects of the impoverished home environment related to poverty, poor education, and poor nutrition also may influence developmental status (Azuma & Chasnoff, 1993).

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In the Coles and colleagues (1992) study, with infants discharged from the hospital within the first few days of life, prenatal cocaine exposure predicted neurobehavioral functioning predominately on the evaluations conducted at 1 month of age. There were few differences in performance between cocaine-exposed and non-exposed controls on evaluations conducted within 3 days of birth and at 14 days of age. By 1 month of age, the cocaine-exposed infant has accumulated experience with the mother and the surrounding environment. Therefore, the direct biochemical effects of prenatal cocaine exposure on neurobehavioral functioning may be difficult to disentangle from other indirect and comorbid effects (Neuspiel, 1995). It is useful, then, to isolate the direct influences of prenatal cocaine exposure as much as possible. One way to accomplish this goal is to examine behavior before the infant has been discharged from the hospital, thereby minimizing the potential effects of the home environment. Examining behavior early in the course of development, however, limits the types of functions that can be assessed due to the immature repertoire of the neonate (Korner, 1989). Moreover, the period of examination may overlap, to some degree, with concurrent exposure depending on how quickly the agent clears physiologically from the neonate's system.

Finally, the majority of studies to date have collected neurobehavioral data at only two time points, inadequate to study the process of change (Bryk & Raudenbush, 1987). Moreover, separate statistical analyses typically were conducted on neurobehavioral performance at each time point, limiting examination of skill change over time. Developmentalists (e.g., McCall, 1977) have promoted the use of longitudinal research to address developmental issues, and the introduction of flexible analytic techniques to assess developmental change (Bryk & Raudenbush, 1987; Willett, 1988) has made this process more feasible and attractive. Growth curve analysis, one such technique, takes advantage of the increased reliability of change assessments when data are collected at more than two time points, thereby increasing the potential for explanation of the developmental processes and deviations (Rogosa & Willett, 1985). These procedures are useful particularly in quasi-experimental research where subjects may be sampled at different times and at unequal intervals (Bryk & Raudenbush, 1987) and, therefore, are well-suited for use with preterm infants who are born at varying times during gestation, or who are differentially ill and not available for evaluation at consistent ages (Kraemer, Korner, & Hurwitz, 1985).

Korner and colleagues (Korner, Brown, Dimiceli, Forrest, Stevenson, & Lane, 1989; Korner, Kraemer, Reade, Forrest, & Dimiceli, 1987) demonstrated that prenatal variables may influence the pattern of neurobehavioral growth in preterm infants. Prenatal cocaine exposure may impact neurobehavior by affecting the level of performance and/or the rate of development to produce unique developmental patterns that can be described in terms of lag, deficit, delay, and rate constructs (Satz, Fletcher, Clark, & Morris, 1981). For example, *in utero* cocaine exposure may impair the level of neurobehavioral performance at a given point in development but may not alter the rate of age-related skill growth, consistent with a lag-delay model (Satz et al., 1981).

The purpose of this study was to investigate the longitudinal impact of prenatal cocaine exposure on early neurobehavioral development in preterm infants. In order to minimize the contribution of home environment, neurobehavioral change was examined while the infant was hospitalized following birth. The effects of prenatal exposure to other substances, namely, alcohol and tobacco, also were examined to understand more completely the effects of cocaine exposure in the context of other common substance exposures.

METHOD

Participants

Two groups of at-risk infants participated in the study: (a) 20 preterm infants born between 28 and 37 weeks of gestation who were exposed to cocaine *in utero* and (b) 20 preterm infants born to women who did not use illicit drugs during pregnancy. Gestational age was determined from information available in the infant and maternal medical charts, including date of last menstrual period, estimated due date from an ultrasound scan conducted prior to 20 weeks gestation, and Ballard scores (Ballard, Novak, & Driver, 1979). Consistent with findings of other studies with neonates, the same medical chart information was not available for all participants. The cocaine-exposed and non-exposed infants were matched on sex, race, gestational age at birth, and type of nursery admission (Intensive Care vs. Well-

Baby). All participants were recruited prospectively and concurrently within 24 hr of delivery from the nurseries of an urban, public hospital. All infants were free from neurologic complications at the time of evaluation.

Drug Use

Information regarding prenatal drug use was obtained from the mother, the medical staff, and the medical records. Within 24 hr of delivery, an interview detailing the quantity-frequency-variability parameters for each substance used during pregnancy was conducted by KAE in a structured format relative to pregnancy landmarks, as advocated by Woods, Behnke, Eyler, Conlon, and Wobie (1995).

Infants who fulfilled the following criteria were included in the study as cocaine-exposed: (a) a positive drug screen for cocaine or its metabolites in meconium and/or urine samples taken from the mother and/or (b) admitted maternal use without a positive drug test result. Urine screening was conducted according to standardized criteria already in place at the hospital.

In order to establish a control cohort of truly non-exposed infants, all mothers who participated in this control group were required to deny illicit drug use during pregnancy and to consent to have 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 for screening. Analysis for the presence of cocaine, marijuana, and opiates was to be conducted on all submitted samples. Although meconium or urine analyses were obtained for all cocaine-exposed infants, meconium or urine analyses were obtained for only 7 of the non-exposed infants. Four meconium samples had been collected too late after birth to be useful (i.e., transitional stool). The laboratory lost the remaining meconium samples from the non-exposed infants ($n = 9$). Because women who consented to infant meconium testing were apprised fully of the nature and sensitivity of meconium testing prior to giving consent, it is assumed that women would not have agreed to meconium collection and risk detection of prenatal substance use if they had used drugs during pregnancy and denied drug use on questioning. Urine screening of the 7 non-exposed infants was negative. Moreover, Bibb, Stewart, Walker, Cook and Wagener (1995) demonstrated that only 3.4% of women delivering in this same hospital (with some overlap of recruiting periods) used cocaine, with no difference obtained between maternal self-report and meconium sampling methods. It was deemed reasonable, therefore, to assume that the non-exposed cohort was, in fact, free from illicit drug exposure.

Predictor Measures

Prenatal cocaine exposure status and the amount of prenatal alcohol and tobacco exposure were included as predictors in models of change, according to the methods described in Francis, Fletcher, Steubing, Davidson, and Thompson (1991). Maternal cocaine, alcohol, and tobacco use information is presented in Table 1. Use of illicit drugs other than cocaine occurred too infrequently to be included in the analyses. Five cocaine-abusing women reported marijuana use

TABLE 1
Maternal Drug Use Information

	Drug		
Variable	**Cocaine (n=20)**	**Alcohol (n=15)**	**Tobacco (n=22)**
Preferred Administration Route (%)			
Injection	35		
Inhalation	45		
Insufflation	20		
Frequency of Use (%)[a]			
1X month	5	13	0
1–3 X month	15	33	0
1X week	35	27	0
>1 X week	45	27	100
Trimester Used (%)[a]			
First	90	100	100
Second	85	75	100
Third	85	47	95
Amount of Use (%) [a,b]			
Light	—	100	82
Moderate	—	0	18

Notes: [a] For consumers only.

[b] Amount of cocaine was not estimable reliably. Categorical amount for alcohol (Streissguth et al., 1976) and tobacco (Jacobson et al., 1984) use in oz AA/day and the average number of cigarettes per day, respectively.

during pregnancy. Barbiturate use was reported by 4 women, codeine and heroin use each were reported by 2 women, valium and talwin use each were reported by 1 woman. Four women used only cocaine during pregnancy as determined by self-report and urine analysis.

Cocaine

Exposure status was coded dichotomously as positive if there was evidence of cocaine exposure. Reliable quantity estimations of cocaine exposure were not possible due to (a) the difficulty that these women had in estimating the amount of cocaine used, (b) the variability in the purity of cocaine in the purchased product, and (c) the differential routes of drug administration. Eighty-five percent of the cocaine-abusing women used cocaine throughout pregnancy, with a modal frequency of use greater than once a week.

Alcohol

The average ounces of absolute alcohol consumed per day (oz AA/day) represented the amount of in utero alcohol exposure in order to predict change in neurobehavioral skills. Ounces AA/day was calculated by the method described in Jessor, Graves, Hanson, and Jessor (1968) from the information obtained during the maternal interview. This measure was chosen because of high test-retest reliability reported by Streissguth, Martin, and Bluffington (1976). The majority of alcohol-using women drank alcohol throughout the first two trimesters with a modal frequency of less than once per week. All women were infrequent to light drinkers, consuming less than .49 oz AA/day (Streissguth et al., 1976), with the range of consumption from .01 to .31 oz AA/day.

Tobacco

A similar composite variable of the amount of exposure was calculated for tobacco, but with the number of cigarettes/day representing the quantity variable used for change prediction. The majority of women smoked throughout pregnancy and were classified as light smokers, using less than a pack of cigarettes/day (Jacobson, Fein, Jacobson, Schwartz, & Dowler, 1984), with a range of use of 2.6 to 32.2 average cigarettes/day.

Outcome Measures

Neurobehavioral development was assessed with the *Neurobehavioral Assessment of the Preterm Infant* ([NAPI] Korner & Thom, 1990). This instrument was chosen because of its psychometric properties and specific design for longitudinal use with preterm infants. The NAPI can be administered when the infant is healthy enough to be handled and has been validated for use through 37 weeks conceptional age (birth gestational age + chronological age) (Korner & Thom, 1990). The invariant, standardized sequence of alerting and calming maneuvers has been demonstrated by Korner et al. (1987) to lead to a methodologically rigorous and complete administration for each infant. The NAPI was developed specifically to monitor changes in neurobehavioral performance over time (Korner et al., 1989; Korner et al., 1987). The advantages of the NAPI include a priori determination of item inclusion and behavioral cluster derivation, based on conceptual and statistical cohesion and reliability. The NAPI cluster scores have been shown to have adequate test-retest correlation (r = 0.60 or better). The NAPI consists of seven cluster scores, encompassing three broad domains. The Motor Development and Vigor, Popliteal Angle, and Scarf Sign clusters represented different aspects of neonatal motor skills. The Visual and Auditory Alertness and Orientation cluster was used as a single index of neonatal attention skills. The Irritabilty, Cry Quality and Asleep Percentage clusters represented different aspects of neonatal state behavior.

Procedure

Neurobehavioral assessments were conducted by KAE, who had received training and certification in administration and scoring of the NAPI from Dr. Korner and her staff. It was not possible for the examiner to remain blinded to the exposure status of the infant. Preterm infants are required to be in close proximity to medical equipment for health reasons. These infants, therefore, could not be removed from the nursery for testing so that repeated contact with nursing personnel and family members could not be avoided (e.g., Mayes et al., 1993). There was, however, an overlap of infants in the hospital at any one time, reducing the likelihood that knowledge about a particular infant influenced neurobehavioral test results over time (Korner et al., 1987). Periodic, informal reliability checks were conducted with MLR who was blinded to the exposure status of the infant. No differences of greater than a half point were observed.

All infants were evaluated in the hospital nursery, in an isolette or in an open crib under a warmer. Because the assessment involved handling and removal of the infant from the heat source for a brief period of time, infants could not be tested while on a respirator or while connected to intravenous lines. Evaluations were conducted approximately one hour before feeding in order to decrease the influence of behavioral state on infant performance.

The testing was conducted daily for each infant while the infant was hospitalized, as medical condition permitted. A daily assessment schedule was used in order to collect multiple data points per participant and to provide a robust estimation of neurobehavioral change during the developmental period of greatest change and instability (Korner, Constantinou, Dimiceli, Brown, & Thom, 1991). In order to minimize stress to the earlier-born infants, the nursery staff requested that these infants be assessed every 2 to 3 days. The first assessment was conducted at least 24 hr after birth. Male infants who were circumcised on a given day were not evaluated until the next day.

A total of 173 NAPI evaluations were conducted by a single examiner in order to reduce examiner-related performance differences (Jacobson et al., 1984; Korner et al., 1991). The cocaine-exposed infants received from 1 to 13 evaluations (M = 4.80, SD = 3.30). The average conceptional age for the cocaine-exposed infants on the initial evaluation was 35.5 wk (SD = 1.7) and for the final assessment, 36.4 wk (SD = 1.3). The non-exposed infants received from 2 to 9 evaluations (M = 3.80, SD = 2.50), with the average conceptional ages at initial evaluation of 35.1 wk (SD = 2.1) and at final evaluation of 35.9 wk (SD = 1.7). No group differences

were found in the mean number of evaluations or in the mean conceptional age at the initial or final evaluation.

Assessments were conducted ranging from 1 day to 55 days of age. The average chronological age at the final assessment was 15 days (SD = 13) for the cocaine-exposed infants and 11 days (SD = 10) for the non-exposed infants. There were no group differences in the mean chronological age at the final evaluation. Ninety-two percent of all evaluations were conducted within the first 4 weeks after birth.

ANALYSIS

Growth curve analysis was used to analyze the longitudinal data. Conceptually, these analyses can be considered to consist of two phases—the individual (within-subject) and the group (between-subject)—although analyses were carried out simultaneously. Individual growth curves were calculated by regressing respective NAPI cluster performance on age since conception in order to estimate the parameters of the within-subject model.[1] From these individual curves and corresponding estimated parameters, aggregate group curves were derived where the performance level and the growth rate were expressed in terms of between-subject variables (e.g., prenatal cocaine exposure status). The individual growth curve for each infant can be specified by the following model:

$$Y_{it} = \pi_{0i} + \pi_{1i} * A_{it} + R_{it} \quad (1)$$

where Y_{it} is the cluster performance for infant i at time t; π_{0i} is infant i's intercept parameter, which is the expected performance for infant i when age equals 0; π_{1i} is the slope of the line relating performance to age for infant i (as such, π_{1i} describes the rate of performance change over the observation period); A_{it} is age since conception for infant i at time t; and R_{it} is random error.

The intercept of the individual growth curve represents the infant's expected performance when age is at zero in the growth model. Consequently, intercept values and their variance depend on the conceptional age at which the age data in the model have been centered (i.e., depending on the conceptional age that has been set to equal zero). Any value may be chosen around which to center the data. For example, centering age at 40 weeks conceptional age implies that the intercept parameter in Equation 1 represents the expected level of neurobehavioral performance for infant i at delivery due date. In the analyses reported here, age was centered at 36 weeks conceptional age.

Developmental hypotheses were examined using a mixed models approach with restricted maximum likelihood estimation procedures. PROC MIXED from SAS version 6.08 was employed. The statistical analysis consisted of two phases: (a) an unconditional model was used to examine the mean and variance of the within-subjects parameters, and (b) four a priori conditional models were estimated to account for the variance in the within-subject parameters. All models were fit for each outcome variable separately. Significance tests for both means and variances of the individual growth parameters were conducted.

The procedures used to specify the models are described in Thompson et al. (1994). The unconditional model included an intercept representing an infant's expected cluster score at the 36 weeks conceptional age and a linear trend representing the constant rate of change (i.e., the slope of the growth trajectory). All analyses were conducted with the data centered at 36 weeks conceptional age. Thirty-six weeks conceptional age was inside the range of the data for most of the infants and represented the age around which the majority of the preterm infants would be expected to be discharged from the hospital. Chronological age, by itself, was not used to center the data because the extant body of literature has shown that neurobehavioral performance is determined by conceptional age, that is, birth gestational age plus chronological age (Korner et al., 1987; Korner et al., 1989).

Initially, the parameters of Equation 1 were allowed to vary across participants when the variance test yielded a probability of less than .20. A probability cut-off of .20 (instead of .05) increased the level of certainty that growth parameters did not vary randomly (Hunter & Schmidt, 1990). Differences between cocaine-exposed and non-exposed infants were examined for intercepts and slopes regardless of the results of these variance tests. However, if variability in the parameter was judged to be non-significant, the mean value of the parameter was tested. If the mean value of the growth parameter differed from zero, the parameter was retained in the model, but the residual variance was fixed at zero. In that case, the growth parameter is concluded to have a nonzero value in the population, but participants are presumed not to differ in their value of the parameter. When the mean value of the parameter and its variance were judged not to differ from zero, the parameter was deleted from the model.

For the second phase of analysis (the between-subjects or group phase), four conditional a priori models were fit that examined the influences of the predictor variables on the average performance level and the average rate old-related performance change. These models were fit in order to isolate the singular contributions of prenatal cocaine exposure, and the amounts of prenatal alcohol and tobacco exposure on neurobehavioral development, respectively, as well as the effects of the single exposure in the context of the other substances. This goal was accomplished by entering each substance into a model as the only predictor. Therefore, there were three singular models with one predictor: prenatal cocaine exposure status, the amount of prenatal alcohol exposure, and the amount of prenatal tobacco exposure. In the fourth model, prenatal cocaine exposure status, and the amounts of prenatal alcohol and tobacco exposure were entered together, as a block, in a single model (contextual).

RESULTS

Descriptive Statistics

Maternal and infant demographic characteristics of the cocaine-exposed and non-exposed infants are presented in Table 2. Cocaine-abusing and non-abusing women differed in age at delivery, with more teenage mothers in the non-abusing group, $\chi^2(1, N = 40) = 4.44$, $p < .04$. There were 4 non-abusing mothers and no cocaine-abusing mothers under 18 years of age at delivery. The number of women who used alcohol or tobacco during pregnancy differed by

TABLE 2
Demographic Characteristics of Cocaine-Exposed and Non-Exposed Preterm Infants

Variable	Exposed (n=20)		Non-Exposed (n=20)	
	Mean	SD	Mean	SD
Birth Gestational Age (weeks)	34.35	2.66	34.35	2.72
Birth Weight (gm)	2121.00	617.53	2316.10	655.06
Birth Head Circumference (cm)	30.40	2.41	31.60	1.96
Hospital Days	16.75	16.35	11.90	13.61
Maternal Age**	29.60	6.34	21.70	4.94
Maternal Education	11.45	1.36	11.10	1.74
Tobacco use during pregnancy [a]	11.37	8.49	6.52	2.36
Alcohol use during pregnancy [b]	0.10	0.09	0.08	0.07

Note. ** $p < .01$.
[a] Cigarettes per day for consumers only (n = 12 cocaine-exposed, 3 non-exposed).
[b] Based on alcohol consumption for consumers only and reported in terms of absolute alcohol per day by method described in Jessor et al. (1968) (n = 17 cocaine-exposed, 5 non-exposed).

infant group, Alcohol $\chi^2(1, N = 40) = 8.64, p < .01$, Tobacco $\chi^2(1, N = 40) = 14.56, p < .01$. Twelve cocaine-abusing women and 3 non-abusing women used alcohol during pregnancy and 17 cocaine-abusing women and 5 non-abusing women used tobacco during pregnancy.

Unconditional Model: Means and Variances of the within-subject Parameters

Motor Domain

The results from the unconditional models, the first stage of analysis, are presented in Table 3. The mean intercept estimate for the Motor Development and Vigor (MDV) cluster score was 71.1 points. This value represents MDV cluster performance at 36 weeks conceptional age for all infants, regardless of exposure status. The estimated mean MDV cluster slope parameter ($\mu_{\pi 1}$) was 9.9, which differed from zero, indicating a constant rate of improvement with age. An infant would be expected to gain 9.9 MDV cluster points per week of conceptional age. Results for the Popliteal Angle (POP) and Scarf Sign (SCF) clusters were similar to those for the MDV cluster, revealing non-zero performance at 36 weeks conceptional age and constant growth with age.

There was significant variability in all motor intercept parameters, indicating that the level of motor skill at 36 weeks conceptional age differed among infants. In contrast, the variance in the MDV and POP cluster slope parameters was very small and could not be estimated reliably. The variance in the SCF slope parameter was not statistically significant. Therefore, the rate of change in motor skill was considered to be constant among infants.

Attention Domain

Expected performance on the Visual and Auditory Alertness and Orientation (AO) cluster was estimated to be 48.0 points at 36 weeks conceptional age, regardless of exposure status. The average rate of age-related change in attention skills did not differ significantly from zero. Subsequent regression analyses revealed that the slope parameter estimates differed between the cocaine-exposed and non-exposed infants, $F(1, 131) = 6.12, p < .01$. The slope parameter, therefore, was retained in the model.

There was significant variability in the intercept parameter, suggesting that infants differed in the level of attention skill at 36 wk conceptional age. However, the variance in the slope parameter was nonsignificant. Visual inspection of the individual growth curves (where the AO cluster score was plotted against conceptional age) revealed that AO cluster performance was variable at contiguous time points for the majority of infants. These results are not surprising given that evaluations were conducted daily, and infant alertness is highly variable (Korner & Thom, 1990).

TABLE 3
Results of the Unconditional Model

Outcome Measure	M	SE	Estimated Parameter Variance
MDV Intercept	71.1**	2.9	152.7**
MDV Slope [a]	9.9**	1.2	—
POP Intercept	74.8**	2.8	186.5*
POP Slope [a]	3.1**	1.3	—
SCF Intercept	85.0**	1.9	97.4**
SCF Slope [a]	4.7**	0.9	—
AO Intercept	48.0**	2.5	144.3*
AO Slope [a]	0.8	1.2	—
IRR Intercept	47.5**	3.3	270.3**
IRR Slope [a]	6.8**	1.5	—
CRY Intercept	82.5**	3.5	327.1**
CRY Slope [a]	7.1**	1.8	—
ASP Intercept	24.7**	2.5	145.9*
ASP Slope [a]	-2.8*	1.4	—

Note. Intercept parameter is the average level of performance at 36 weeks conceptional age.

[a] Variance in the slope parameters was fixed due to lack of significant parameter variance across subjects.

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

State Domain

The mean values at 36 wk conceptional age, on the Irritability (IRR), Cry Quality (CRY), and Asleep Percentage (ASP) clusters were 47.5, 82.5, and 24.7 points, respectively, regardless of exposure status. The average rates of age-related growth differed significantly from zero for all state clusters. The rate of change in the percentage of time asleep during the evaluations was negative, reflecting greater arousal with age.

There was significant variability in the IRR, CRY, and ASP intercept parameters, indicating that the level of state regulation skill at 36 weeks conceptional age differed among infants. However the variance in the IRR, CRY, and ASP slope parameters was too small to be estimated reliably. Therefore, developmental growth in state regulation was considered to be constant among infants.

Conditional Models: Predictors of Within-Subject Parameters

Motor Domain

The results of the between-subjects conditional models for performance on the MDV, POP, and SCF clusters are presented in Tables 4 and 5. The amount of prenatal alcohol exposure predicted rate of age-related change in MDV cluster performance when considered singularly (i.e., as a single predictor, see Table 4) and in the context of additional prenatal substance exposure (i.e., as one of multiple predictors, see Table 5). An exposure to .10 oz AA/day of alcohol during gestation was associated with an increase in the growth rate of MDV performance of 5.59 points per conceptional week (See the pertinent Alcohol x Slope parameter in Table 4). The rate of motor development on the POP and SCF clusters also was related to the amount of prenatal alcohol exposure, in the context of additional prenatal substance exposure. When considering exposure to alcohol in the context of other substance exposure, an exposure of .10 oz AA/day of alcohol prenatally was related to increased rates of change in motor skills of 4.00 (SCF) to 7.54 (MDV) cluster points per conceptional week (see slope parameters associated with each substance in Table 5). The growth rate of POP and SCF skills tended to be related to the amount of prenatal alcohol exposure when analyzed singularly, $p < .09$ for both.

TABLE 4
Results for Conditional Models with Single Predictor

	MDV		POP		SCF		AO	
	γ	SE	γ	SE	γ	SE	γ	SE
Model for Cocaine Exposure								
Intercept	73.30**	4.07	77.73**	4.06	84.67**	2.88	52.49**	3.42
Cocaine	−5.62	5.61	−5.65	5.61	0.42	3.95	−9.34*	4.65
Slope	7.58**	1.66	3.30	1.76	4.30**	1.24	−0.87	1.48
Cocaine X								
Slope	4.34	2.31	−0.04	2.62	1.03	1.03	4.54*	2.24
Model for Alcohol Exposure								
Intercept	72.19**	2.90	74.90**	3.03	84.72**	2.11	47.97**	2.92
Alcohol	−7.78**	3.22	−2.74	3.32	−1.13	2.34	−2.62	3.24
Slope	7.21**	1.29	2.11	1.42	3.95**	0.99	−0.12	1.38
Alcohol X								
Slope	5.59**	1.56	3.26	1.96	2.20	1.35	−0.60	1.89
Model for Tobacco Exposure								
Intercept	73.54**	3.59	74.84**	3.49	83.84**	2.40	48.16**	3.25
Tobacco	−0.53	0.38	−0.01	0.37	0.17	1.10	−0.13	0.34
Slope	8.19**	1.50	3.06*	1.60	4.30**	0.25	−0.60	1.50
Tobacco X								
Slope	0.29*	0.15	0.11	0.18	0.07	0.12	0.31	0.17

Notes. γ is the relevant parameter estimate. The intercept parameter is the average level of performance at 36 weeks conceptional age.
* $p < .05$, ** $p < .01$.

The amount of prenatal alcohol exposure, when considered singularly or in the context of other substance exposure, predicted the level of MDV performance at 36 weeks conceptional age. Exposure to .10 oz AA/day of alcohol during gestation was associated with an decrease in the level of motor skill (−7.78 MDV cluster points in the singular model, −8.22 MDV cluster points in the contextual model). The amount of prenatal alcohol exposure, however, did not significantly affect the level of POP and SCF performance at 36 weeks regardless of whether additional prenatal substance exposure was controlled. However, the magnitude of the effect of the amount of prenatal alcohol exposure was negative for both variables in the singular and contextual models. Neither *in utero* cocaine or tobacco exposure predicted the level of motor performance or the rate of motor skill development.

Attention Domain

The results of the conditional model for the Visual and Auditory Alertness and Orientation (AO) cluster also are depicted in Tables 4 and 5. In both the single and multiple predictor models, prenatal cocaine exposure predicted the expected AO cluster score. Prenatal cocaine exposure was associated with a decrease of 9.34 AO cluster points at 36 weeks conceptional age. Additional prenatal substance exposure increased the magnitude of the effect of prenatal cocaine exposure on the expected level of AO performance by 3.54 points, indicating that the inclusion of other substance exposure in the model potentiated the negative impact of cocaine exposure on attention performance.

The rate of age-related change in AO cluster performance was predicted by prenatal cocaine exposure, but only in the singular model. Prenatal cocaine exposure did not predict the rate of change in AO performance when considered in combination with exposure to alcohol and tobacco, indicating that the relation of prenatal cocaine exposure and the rate of attention skill development may be spurious.

State Regulation Domain

The results of the conditional models for the Irritability (IRR), Cry Quality (CRY), and

TABLE 5
Results for Conditional Models with Multiple Predictors

	MDV		POP		SCF		AO	
	γ	SE	γ	SE	γ	SE	γ	SE
Effects on Intercept Parameter								
Intercept	72.16**	3.81	76.05**	4.10	83.66**	2.87	51.76**	3.74
Cocaine	−2.21	6.11	−6.85	6.54	−1.46	4.56	−12.88*	5.90
Alcohol	−8.22*	4.26	−5.48	4.82	−4.23	3.24	−3.37	4.21
Tobacco	0.14	0.51	0.52	0.58	0.49	0.38	0.57	0.49
Effects on Slope Parameter								
Slope	6.30*	1.58	3.03*	1.76	4.10*	1.23	−0.90	1.60
Cocaine	5.30	3.08	1.65	3.59	1.43	2.48	4.14	3.26
Alcohol	7.54**	2.27	7.41*	3.17	−4.00*	2.01	2.58	2.88
Tobacco	−0.45	0.27	−0.58	0.36	−0.27	0.24	−0.10	0.32

Notes. γ is the relevant parameter estimate. The intercept parameter is the average level of performance at 36 weeks conceptional age.
* $p < .05$, ** $p < .01$.

Asleep Percentage (ASP) clusters were non-significant with one exception, indicating that prenatal substance exposure was unimportant in determining the development of state regulation skills in preterm infants.[2] Only the amount of prenatal exposure to alcohol predicted the rate of change in IRR cluster performance, and only when considered singularly.

DISCUSSION

The results from this study indicate that developmental outcome in preterm infants differs depending on whether the infant was exposed to cocaine or alcohol in utero and the neurobehavioral domain examined. Prenatal cocaine exposure was related to attention deficits at 36 weeks conceptional age of approximately 0.66 of a standard deviation according to normative data (Korner & Thom, 1990), even when other *in utero* substance exposure was considered. Because prenatal cocaine exposure did not predict the rate of attention development, the cocaine-related difference in attention skill did not improve with age. This developmental pattern can be described by a deficit-delay (Satz et al., 1981), in which the reduction in the final level of performance does not change with conceptional age.

In contrast, prenatal alcohol exposure was associated with increased rates of motor development. Prenatal alcohol exposure also negatively impacted the level of performance on the MDV cluster at 36 weeks conceptional age. Taken together, these findings suggest that in utero alcohol exposure retards motor competence in preterm infants. When the deleterious effects of alcohol are removed through termination of exposure by birth, preterm alcohol-exposed infants "make-up" this performance impairment to reach their expected level of motor proficiency by 36 weeks conceptional age. For alcohol, the developmental process can be viewed as compensatory with lag-delay-rate influences; that is, faster neurobehavioral skill development to adjust for the alcohol-related skill reductions (Satz et al., 1981). However, the relatively low quantity of alcohol consumed by women in this sample prevents generalization to infants exposed to higher amounts of alcohol.

The observed developmental pattern also suggests that changes in performance immediately after birth may differ substantively from changes in performance at 2–4 weeks chronological age. Because neurobehavioral performance was examined close to birth in some infants, this developmental pattern may result, in part, from the abused substance not having been cleared completely from the neonatal physiology at the time of evaluation. Because cocaine and alcohol are metabolized rapidly in neonates (Saxon, Calsyn, Haver, & Delaney, 1988), and many infants were not available for evaluation until several days after birth due to ongoing health concerns, this explanation may

be relevant for only a few infants. One advantage of the longitudinal design is that the impact of any particular evaluation is reduced relative to the overall growth trajectory.

Alternatively, the increased rate of motor skill change for the lower functioning infants may be a measurement artifact; that is, points may be more easily gained at lower levels of the scale. Each of these interpretations suggests that change is nonlinear, although in the latter case, this nonlinearity is strictly a consequence of measurement and not development. The present study did not show statistically that growth in motor proficiency was nonlinear. However, the power to detect nonlinearity may have been insufficient.

Alcohol negatively affected MDV skills, but not POP and SCF abilities, at 36 weeks conceptional age. By traditional ANOVA methods, post-hoc power analysis of the POP cluster, for example, revealed that the likelihood of detecting a difference of -2.74 cluster points was .71, consistent with slightly reduced power. However, the developmental time course among motor clusters also may differ, such that the conceptional age at which MDV cluster performance is comparable among alcohol-exposed and non-exposed infants is greater for the MDV cluster than for the POP and SCF clusters.

A larger sample size and/or longer follow-up would be necessary to distinguish among these alternatives. The estimated mean NAPI performance levels were comparable with normative data derived from much larger samples (Korner & Thom, 1990), suggesting that this sample adequately reflects preterm infants at large. Furthermore, institution of a longer follow-up period would necessitate conducting evaluations post hospital discharge, thereby adding variability related to environmental influences but permitting assessment of a wider range of behavioral abilities.

These results extended those of other researchers who observed neurobehavioral deficits in fullterm cocaine-exposed neonates to preterm infants (Chasnoff et al., 1985; Eisen et al., 1991; Mayes et al., 1993; Neuspiel et al., 1991). These findings also illustrate the advantage of using growth curve analysis in order to clarify how in utero substance exposure alters the course of development, through impact on both performance level and growth rate parameters.

It is necessary to consider the effects of other substances, particularly alcohol, when examining the effects of prenatal cocaine exposure on neurobehavioral development. In contrast to findings for fullterm infants (Coles et al., 1992), the negative impact of in utero cocaine exposure on attention abilities was prominent during the lying-in period for preterm infants in this study. The neurobehavioral effect of prenatal cocaine exposure observed after hospital discharge at 28 days chronological age in the Coles et al. (1992) study may have been influenced, in part, by the deleterious indirect and/or comorbid effects related to the home environment (Brinker et al., 1994; Woods et al., 1993). The ability of this study to detect attention deficits may be partially a consequence of the minimization of these effects through hospitalization. Although the quality of neonatal nursery care is a debated topic (Als & Gilkerson, 1995), at a minimum, the infant's biological needs are met in the nursery in a manner of which a substance-abusing parent may not be capable.

Despite the attraction of linking neonatal cocaine-related attention deficits with apparently similar cognitive disturbance at older ages, neonatal neurobehavior may or may not be related to subsequent developmental outcome (Brazelton, 1990; Rose & Feldman, 1995). The deleterious effects of prenatal substance exposure on ability may change with maturation. Goldman (1974) used the principle of "functional heterology" to describe the developmental course of deficit production in monkeys with experimentally-induced brain insults. Depending on the nature and site of brain damage, deficits were produced initially, followed by recovery of function, and then, subsequent deficits resurfaced with further development. This behavioral sequence was considered a consequence of different brain areas subsuming different cognitive functions with advancing age. Brain structures compromised by prenatal substance exposure may underlie neonatal neurobehavioral responsivity and also may subsume related competencies later in development. However, such consistent brain-behavior relations across the age spectrum are not easily inferred from behavioral observations alone (Diamond, 1991). This study examined behavior during the neonatal period, a very restricted age range, limiting conclusions about subse-

quent developmental periods and later behavioral competencies.

These findings also must be interpreted in light of the difficulty in estimation of conceptional age in at-risk samples, particularly in infants born to substance-abusing women. Conceptional age is biased if birth gestational age is not known reliably. Although inherent unreliability in conceptional age estimates exists, the chaotic life style associated with substance abuse may be related to greater difficulty reliably recalling the last menstrual period. This problem reflects limitations of all investigations of infants who have been exposed to various substances *in utero*, but is particularly important in this study because the growth curves are dependent on accurate gestational age assessment. This study, however, has illustrated the potential to detect the developmental effects of prenatal cocaine and alcohol exposure on neurobehavior in hospitalized preterm neonates.

Authors' Notes

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Footnotes

1. SAS Proc Mixed uses a weighted average of the individual and group estimates to determine the parameters of the growth curves. This approach takes what data are available for a given participant to derive the parameter estimates and the information used for estimation is weighted optimally, based on precision. For the cocaine-exposed infant with only one evaluation, the estimation of the growth curve parameters, therefore, is weighted fully to the average growth parameters of the cocaine-exposed group. The parameter estimates for an infant with many data points spread evenly across conceptional age would be weighted more heavily towards the individual trajectory.
2. These results are available from the first author.

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