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Neurobehavioral outcomes of cocaine-exposed infants

Lynn T. Singer[a,*], Robert Arendt[a], Sonia Minnes[a], Kathleen Farkas[b], Ann Salvator[a]

[a]*Department of Pediatrics, Case Western Reserve University School of Medicine, Suite 250-A, The Triangle Building, 11400 Euclid Avenue, Cleveland, OH 44106, USA*

[b]*Mandel School of Applied Social Sciences, Case Western Reserve University, Cleveland, OH, USA*

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Abstract

The present study investigated the neurobehavioral outcomes of fetal cocaine exposure. Attempts were made to control, by design or statistical analysis, for significant confounders. Timing and amount of drug exposures were considered, and biologic measures of exposure were quantified to classify exposure severity. One hundred sixty-one non-cocaine and 158 cocaine-exposed (82 heavily and 76 lightly exposed) infants were seen at a mean-corrected age of 43 weeks post-conception and administered the Neurobehavioral Assessment (NB Assessment). Heavily cocaine-exposed infants had more jitteriness and attentional problems than lightly and non-exposed infants. They also had more movement and tone abnormalities, and sensory asymmetries than non-exposed infants. Heavily exposed infants were more likely to be identified with an abnormality than non-exposed infants and there was a trend toward heavily exposed infants being more likely to be identified with an abnormality than lightly exposed infants. Furthermore, there was a trend for heavily exposed infants to be less likely to be testable than non-exposed infants. After the confounding and mediating factors were considered, heavily cocaine-exposed infants were four times as likely to be jittery and nearly twice as likely to demonstrate any abnormality than lightly and non-exposed infants, but all other effects were no longer significant. Higher concentrations of the cocaine metabolites of cocaine, cocaethylene, and benzoylecgonine (BZE) were related to higher incidence of movement and tone abnormalities, jitteriness, and presence of any abnormality. Higher cocaethylene levels were related to attentional abnormalities and higher *meta*-hydroxybenzoylecgonine (*m*-OH-BZE) was related to jitteriness. Drug effects on attention were mediated by maternal psychological distress, suggesting that this factor should be considered in future studies of drug exposure effects.

Keywords: Cocaine; Neonatal behavior; Attention; Drugs; Maternal distress; Marijuana; Alcohol; Cigarettes; Motor development; Teratology

The nature and extent of the effects of fetal cocaine exposure on child developmental outcomes have been the focus of recent longitudinal investigations. Because cocaine can cross the placental barrier [47], is known to have specific effects on catecholinergic neurotransmitters [64,65], can produce vascular changes and hypoxia in the fetus [67,68], and has been associated with poorer fetal growth [9,32,41,55,71], concerns have also been raised about deleterious neurobehavioral sequelae [57].

Many studies have used the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) [5] to assess the early neurobehavioral functioning of cocaine-exposed neonates, with markedly disparate results. In those studies with larger sample sizes (>30), a wide variety of negative sequelae has been identified in the early neonatal period, including deficits in autonomic stability [46,62], orientation [7,12], state regulation [46], motor activity [6,7,12,46], and habituation [7,34]. Almost as many studies have found no effects [16,34,39,44,45,64] when the standard BNBAS categories were used.

There are significant methodological differences and shortcomings among these studies which have been described in detail by Richardson et al. [46]. These include differences in populations, proportions of preterm infants included, method of drug screening, timing of testing, infant age at administration, and variations in control for confounders, including other drugs, sociodemographic differences, and examiner effects. These differences and methodologic weaknesses make interpretation of the findings of these studies difficult to reconcile, since there is little consistency even among those studies with positive findings regarding

* Corresponding author. Tel.: +1-216-844-6212; fax: +1-216-844-6233.

E-mail address: lxs5@po.cwru.edu (L.T. Singer).

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the specific BNBAS behavioral domains which are affected by cocaine exposure.

The two largest studies to date using the BNBAS [16,46] differ in their findings and also in their methodology. Eyler et al. [16] compared 154 full-term infants of rural cocaine users with an equivalent number of controls matched for race, parity, socioeconomic status, and pregnancy risk. The BNBAS was administered at 3–5 days after birth, on average, corrected for prematurity. There were no differences based on the standard BNBAS clusters, but there were significant findings of poorer performance on the qualifier scores of alert responsiveness, examiner persistence, general irritability, regulatory capacity, state regulation, and reinforcement value of infant's behavior. These differences, with the exception of alert responsiveness, were no longer significant after control for other drug confounders. When the timing and amount of drug exposure were considered, amount of cocaine used in the third trimester was related to poorer state regulation, after control for other drugs and their interactions. Maternal age, education or amount of prenatal care were not controlled.

In the Richardson et al. [46] study, 115 non-exposed infants were compared to 44 infants exposed to occasional (<1 line/day) and 37 exposed to frequent (≥1 line/day) cocaine use on the BNBAS on the second and third days after birth. All were full term, and confounding drug and demographic variables were statistically controlled. Effects of cocaine were found on the autonomic stability, motor maturity and tone scores, and the number of abnormal reflexes on day 2, but not on day 3. By day 3, effects were found only for range of state.

Another large prospective study [6] using a different instrument, the Neurobehavioral Assessment of the Preterm Infant (NAPI) [28], examined 119 cocaine/polydrug-exposed infants, 19 alcohol-only-exposed and 97 non-exposed infants. Preterm infants, who comprised more than half the sample, were seen at 36 weeks conceptional age while full-term infants were seen within 1–3 days postpartum. After control for other factors, cocaine/polydrug exposure predicted poorer orientation and greater irritability. A relationship was found between frequency of cocaine use during pregnancy and poorer motor scores, after control for social risk and gestational age.

Several investigations have examined neurobehavioral outcomes on the BNBAS beyond the first 72 h. Woods et al. [69] found no effects at 1 month after birth, but had 43% attrition, while Neuspiel et al. [39] found poorer motor outcomes, which were non-significant after controlling for some confounders. Coles et al. [12], however, found a cocaine/alcohol effect on reflexes at 14 days, and a cocaine effect on motor activity, reflex abnormalities, and state regulation at 1 month. Similarly, Tronick et al. [62] found abnormal reflexes, poorer state regulation, and poorer autonomic stability at 16 days in a cocaine-exposed sample. In a separate report with unknown overlap in subjects, in contrast, Tronick et al. [63] reported no differences on the BNBAS qualifier scores at 2–3 weeks of age among heavily exposed, lightly exposed and unexposed infants, but found effects of heavy exposure on excitability and state regulation.

Using an experimental visual recognition memory task, Singer et al. [53] assessed 75 heavily exposed cocaine positive infants, 56 lightly exposed, and 136 non-exposed infants at a mean corrected age of 3 weeks. About 30% of the sample was preterm. After control for a large number of potential confounders, including maternal psychological distress, heavily exposed infants performed more poorly than non-exposed infants, suggesting deficits in early visual attention, discrimination, and memory.

A methodologic problem of all studies in which infants were seen in the first 72 h postpartum is that none has controlled for the effects of drugs of labor and delivery on the infant. The only study which reported on the use of obstetric drugs [44] found cocaine-using women more likely to have anesthesia. Thus, effects noted in the immediate neonatal period may be confounded by those of obstetric drugs.

Another methodologic issue of concern is that only a few studies [53,69] of cocaine exposure and infant neurobehavior in the immediate or later neonatal period have addressed the issue of maternal depression or psychological distress, and only one [53] controlled for the possible effects of such symptoms on outcomes. High rates of psychopathology have been found in cocaine-using women [27,35,54,56,69]. In studies of alcohol [24], cocaine [54], and heroin-using mothers [21], and in studies of non-substance-abusing women [51], maternal symptoms of depression or other psychopathology have been associated with poorer child developmental outcomes. Maternal symptoms of depression or psychological distress have also been associated with neonatal neurobehavioral differences [17,70] in non-substance-exposed samples, warranting their investigation in substance-exposed samples.

Thus, beyond the immediate neonatal period, there has been some consistent replication of adverse effects of cocaine exposure on motor and reflex activity, as well as state regulation, when the BNBAS was used. Moreover, poorer neonatal visual recognition memory in cocaine-exposed infants has been demonstrated on an experimental task in a large, well-controlled sample. Several of the reviewed studies have found specific neurobehavioral effects in the neonatal period only at heavier levels of exposure [53,63]. The use of quantitative biologic markers of cocaine dose, such as the amount of cocaine metabolites in meconium, may establish higher levels of exposure more reliably [3,52,53] and thus aid the detection of specific effects of cocaine exposure on neurodevelopment. In many studies, it is also not clear whether confounding drug variables, particularly marijuana, cigarettes, and alcohol, have been quantified. As has been noted by Jacobson and Jacobson [23], failure to reliably measure the effects of

confounders may lead to spurious attribution of effects to cocaine. Finally, the possible impact of maternal psychological stress, especially depression, a factor related to neurobehavioral outcomes in prior studies of both substance exposed and non-exposed samples, has been controlled in only one study [53].

The present study investigated neurobehavioral outcomes associated with fetal cocaine exposure. Attempts were made to control, by design or statistical analysis, for significant confounders noted in the research literature, particularly socioeconomic and prenatal care factors [4,42], severity of exposure to other substances, especially alcohol, marijuana, and tobacco [18,19,24], and other maternal risk factors which may have a direct or indirect impact on neonatal behavior, such as maternal intellectual ability, age, parity, and psychopathology. Both timing and amount of drug exposures were considered, and biologic measures of exposure were quantified to classify exposure status and severity.

1. Method

1.1. Subjects

A total of 415 infants (218 cocaine-exposed, 197 non-exposed) were recruited at birth to participate in a longitudinal study of the sequelae of fetal drug exposure from October, 1994 through June, 1996. All mothers and infants were recruited from MetroHealth Medical Center, a large, urban county teaching hospital in Cleveland, OH, and identified from a high-risk population screened for drug use. Urine samples were obtained immediately before or after labor and delivery and analyzed for the presence of cocaine metabolites, cannabinoids, opiates, PCP, and amphetamines. Urine toxicology screens for drugs are performed by the hospital on all women who received no prenatal care, appeared to be intoxicated or taking drugs, who had a history of involvement with the Department of Human Services in previous pregnancies, or who self-admitted or appeared to be at high risk for drug use after interview by a social worker or medical resident. The Syva Emit method (Syva, Palo Alto, CA) was used for urine analysis. The specificity for benzoylecgonine (BZE) was 99% at a concentration of 0.3 mg/ml. Follow-up thin layer chromatography or gas chromatography analysis was performed for confirmation.

Infants also had meconium drug analyses performed for cocaine and its metabolites, i.e. BZE, *meta*-hydroxybenzoylecgonine (*m*-OH-BZE), cocaethylene, cannabinoids (THC), opiates, PCP, amphetamines, and benzodiazepines [30,40]. Meconium specimens were collected from the newborns' diapers in the hospital by a nurse trained in the research protocol. When available, samples were accumulated over multiple diapers from the same infant. After collection, specimens were stirred for 5 min to insure homogeneity and stored in a refrigerated container. Further details concerning collection of meconium can be found in a separate report [3].

Screening assays were conducted using Abbott Diagnostics polarization immunoassay reagents (FPIA) [31]. Cutoff levels for drugs of interest were: cocaine and metabolites — 25 ng/g; opiates — 25 ng/g; amphetamines — 100 ng/g; phencyclidine — 25 ng/g; tetrahydro-cannabinol — 25 ng/g. Confirmatory assays were conducted using gas chromatography mass spectrometry (GC/MS) operated in electron impact, selected ion monitoring mode [30,31].

A nurse recruiter approached all screened women shortly before or after infant birth. Six hundred forty-seven mothers and their infants were identified, of whom 54 subjects were excluded (20 cocaine-positive, 34 cocaine-negative). Reasons for exclusion included maternal psychiatric history [16], control with no meconium [15], Down syndrome [2], primary heroin user [2], HIV-positive [5], maternal low IQ [1], fetal alcohol syndrome [1], maternal age <19 years [2], maternal or infant medical illness [7], and others [3]. One hundred fifty-five mothers refused to participate (49 positive, 106 negative), and 23 (nine positive, 14 negative) passively refused when they did not come to the enrollment visit. Therefore, 415 women and their infants were enrolled (218 positive, 197 negative). Four infants died before the first visit (three positive, one negative). The Neurobehavioral Assessment (NB Assessment) was given to 319 (158 cocaine-exposed and 161 non-exposed) of 382 infants who came for the initial visit and who were not too sleepy, too fussy, or too old (>50 weeks corrected age) to be administered the assessment during the visit.

Cocaine-exposed infants were identified by a positive response on any of the following measures: infant meconium, urine, or maternal urine positive for cocaine, maternal report to hospital staff or maternal self-report during clinical interview. In order to be a control subject, all of the above indicators had to be negative. Eleven control subjects were retained even though meconium was unavailable since all other screening and follow-up indicated no evidence of use. Women who used alcohol, marijuana, or tobacco during pregnancy were included in both groups. Cocaine-positive infants were sub-divided into heavy and light categories. The heavy classification was determined by meconium screen or self-report indicating use greater than the 70th percentile for the cocaine users. A previous report [3] on the concordance of meconium concentration and maternal self-report measures of heavy vs. light use in the entire sample from which the present cohort was formed indicated that significant positive correlations ranging from 0.32 to 0.57 were found between the severity of cocaine use from maternal self-report and the amount of cocaine, COCETH, BZE, and *m*-OH-BZE detected in the offspring's meconium. For 10 women from the entire sample

who denied cocaine use, but whose infants' meconium screens were positive, self-report data were estimated by assigning the median score for the group (heavy/light) to which they were assigned based on meconium status.

1.2. Procedures

Infants and their biologic and/or foster mothers/caregivers were seen as soon as possible after birth, at which time the caregiver was interviewed regarding drug use. For infants who were in non-maternal care, biologic mothers were seen at a separate visit. An adaptation of the Maternal Postpartum Questionnaire [54,56,59] was used to quantify maternal drug use. For the month prior to pregnancy, and for each trimester of pregnancy, mothers were requested to recall frequency and amount of drug use. For tobacco, the number of cigarettes smoked per day was recorded. For marijuana, the number of joints per day, and for alcohol, the number of drinks of beer, wine, or hard liquor per day was computed with each drink equivalent to 0.5 oz of absolute alcohol. For cocaine, the number of rocks consumed and amount of money spent per day were noted. For each drug, the frequency of use was recorded on a Likert-type scale ranging from 0 (not at all) to 7 (daily use), which was then converted to reflect the average number of days per week a drug was used. The frequency of use was multiplied by the amount used per day to compute the severity of use score for the month prior to pregnancy and for each trimester. This score was then averaged for a total score for the prenatal exposure for each drug.

Demographic and medical characteristics at the time of infant birth were taken from hospital record. These included maternal race, age, gravida, parity, number of prenatal care visits, type of medical insurance, infant Apgar scores, birthweight, length, head circumference, estimated gestational age, and infant small for gestational age status. Microcephaly, defined as head circumference less than the tenth percentile for gestational age, was calculated using Ross Laboratories growth charts. This study was approved by the Institutional Review Board of the participating hospitals, and maternal written informed consent was obtained for infant participation. All mothers/caregivers and their infants were provided transportation to and from the research laboratory if needed and received a stipend of US$35 for participation.

At birth, all infants were scheduled for follow-up and seen for evaluation at the developmental research laboratories of the Department of Pediatrics. At the initial visit, maternal socioeconomic status using the Hollingshead Scale and maternal educational level were calculated. Maternal vocabulary was measured using the Peabody Picture Vocabulary Test — Revised (PPVT-R) [15]. Two subtests of the Wechsler Adult Intelligence Scale — Revised (WAIS-R) [66] were administered, i.e. the Block Design (BD), and Picture Completion (PC) subtests, to obtain estimates of non-verbal intelligence. Mothers were also administered the Brief Symptom Inventory [14] which yields a summary measure of self-reported severity of psychological distress, the General Severity Index (GSI). The Hobel Neonatal Risk Index [22] was computed from chart review by a research nurse practitioner to obtain a measure of neonatal medical complications.

The NB Assessment [20] was administered at a scheduled visit between 37 and 50 weeks corrected age. This exam rates categories of behavior in binary, forced choice fashion as normal (0) or abnormal (1). The procedure, devised by Gardner et al., is a series of tasks which assesses visual and auditory orienting, passive tone and reflexes, head control, and movement quality and tone of extremity movements of the newborn. The NB assessment was chosen because it was developed from an empirical and theoretical framework to evaluate abnormal brain–behavior relationships, which were the focus of interest in this study. The procedure was validated on a diverse sample of 248 newborns at varying degrees of risk for brain injury who were stratified into six groupings based on risk severity. Average inter-observer agreement for abnormal/normal categories was 0.94, and average Cohen's kappa was 0.81 for all categories. A correlation of 0.48 between brain insult and neurobehavioral performance was found. Neurobehavioral performance also differentiated the proportion of infants showing abnormal performance across the six brain injury groups.

Examiners were trained by Dr. Gardner in administration. Four examiners performed the assessment, with inter-rater reliabilities on percent agreements >0.90 for 8% of the sample. Two examiners had PhD degrees, and two had Master's degrees, all with experience in infant assessment. All examiners were masked to the cocaine status of the infant, and were distributed equally between the exposed and non-exposed groups.

1.3. Statistical analysis

Prior to analysis, cocaine, cigarette, alcohol, and marijuana self-report measures, meconium variables, and maternal and caregiver GSI scores, which were positively skewed, were normalized by means of $\log x+1$ transformation. Means and standard deviations are reported in terms of the original distribution, while log transforms were used in analyses.

Cocaine-negative and -positive mothers and infants were compared on demographic variables, frequency and severity of drug use, and infant birth and neurobehavioral outcomes, using t-tests for continuous data and χ^2 analyses for categorical variables. Additional analyses compared those infants who were given the exam vs. those who were not within exposure groups, as well as compared the lightly and heavily exposed with non-exposed groups. ANOVAs or Mantel–Haenszel χ^2 analyses were used to compare the outcomes of the non-cocaine, lightly, and heavily cocaine-exposed infants.

Spearman correlations were used to assess the relationship of severity of prenatal drug exposure to infant outcomes, based on maternal self-report by trimester, and to assess the relationship of the amount of each cocaine metabolite in infant meconium to infant outcomes. Hierarchical logistic regressions were used to evaluate the predictive power of severity of cocaine exposure after control for confounders. Confounders were entered into analyses stepwise hierarchically if they were distributed unequally between groups and were related to the outcome at $p<0.10$ in the following order: race, gender, parity, number of prenatal care visits, maternal age, years of education, marital status, socioeconomic status, vocabulary score, WAIS-R BD and PC scores, and summary measures of cigarette, alcohol, and marijuana exposure by trimester or averaged over pregnancy.

On the final step, severity of cocaine use (none, light, heavy) was entered. If there was a significant relationship of drug to outcome, Apgar scores, Hobel risk score, birthweight, gestational age, birth length, and head circumference were evaluated as potential mediators of cocaine's or other drug's effects. The effects of maternal and caregiver psychological distress (GSI score) were evaluated separately by adding them to the model after other confounders were considered since psychological distress can be both a confounder and/or mediator of cocaine's effects.

2. Results

2.1. Sample characteristics

Demographic and medical characteristics of the cocaine-exposed and the non-cocaine-exposed infants and mothers seen for the NB assessment are presented in Tables 1 and 2. Cocaine-using mothers were older, had more children, and received less prenatal care. The majority of both groups were African–American, of low socioeconomic status and unemployed. Cocaine-using women had less education, lower vocabulary scores, were more likely to be unemployed, less likely to be married, had higher distress scores and were more likely to use other drugs. Cocaine-exposed infants were of lower birthweight, length, head circumference, and gestational age than non-exposed infants and were more likely to be small for gestational age (SGA). There were no differences between heavy and light users on the majority of the demographic, medical, and birth variables considered (see Tables 3 and 4), with the exception of maternal GSI score, with heavier cocaine users having higher scores than light, and light higher than non-users. Current caregiver GSI scores also differed, with heavy users having higher GSI scores than non-users. Moreover, a higher percentage of heavily exposed infants was placed in non-maternal care than lightly exposed infants who were also more likely to be placed than non-exposed infants.

Table 1
Sample characteristics

	Cocaine ($n=158$)		Non-cocaine ($n=161$)			
Maternal	M±SD	Range	M±SD	Range	$t/\chi^2/F$	p
Age (years)	28.8±5	(18–41)	25.6±5	(18–40)	−6.1	0.000
Parity	3.3±2	(1–10)	2.7±2	(1–10)	−2.5	0.012
Gravida	4.7±2	(1–14)	3.7±2	(1–11)	−4.1	0.000
Number of prenatal care visits[a]	6.0±5	(0–25)	8.7±5	(0–25)	18.7	0.0001
Month began prenatal care	4.5±2	(1–9)	3.5±2	(1–9)	−4.7	0.0000
PPVT-R standard score	73.8±14	(40–121)	78.6±15	(41–123)	2.9	0.004
WAIS-R BD score	6.9±2	(1–14)	7.3±2	(1–13)	1.6	0.12
WAIS-R PC score	6.6±2	(3–12)	7.0±2	(2–17)	1.9	0.06
General severity index (mother)	0.82±0.8	(0–3.8)	0.50±0.5	(0–2.9)	−5.0	0.000
General severity index (current caregiver)	0.64±0.65	(0–3.8)	0.47±0.5	(0–2.9)	−2.7	0.008
Race (non-white)	128 (81%)		129 (80%)		0.04	0.84
No prenatal care	24 (15%)		15 (9%)		2.5	0.11
Alcohol use	134 (88%)		101 (63%)		25.7	0.001
Marijuana use	83 (54%)		18 (11%)		66.7	0.001
Tobacco use	136 (89%)		65 (40%)		80.2	0.001
Amphetamine use	4 (3%)		2 (1%)		0.8	0.38
Barbiturate use	2 (1%)		1 (1%)		0.40	0.53
Valium use	20 (16%)		0 (0%)		0.6	0.001
Heroin use	4 (3%)		0 (0%)			0.06
PCP	8 (5%)		0 (0%)			0.001
Maternal employment	9 (6%)		34 (21%)		16.3	0.001
Married	10 (6%)		30 (19%)		11.0	0.001
Low socioeconomic status	153 (98%)		157 (98%)		0.00	0.97
Education < high school graduate	68 (43%)		53 (33%)		3.5	0.06

[a] p adjusted for gestational age.

Table 2
Sample characteristics

Infant	Cocaine (n=158) M±SD	Cocaine (n=158) Range	Non-cocaine (n=161) M±SD	Non-cocaine (n=161) Range	t/χ^2	p
Birthweight (g)[a]	2738±642	(905–3995)	3112±629	(1017–4515)	18.8	0.0001
Gestational age (weeks)	37.8±3	(28–42)	38.7±2	(30–42)	3.2	0.001
Birth length[a]	47.4±4	(34–58)	49.3±3	(37–57)	11.7	0.0007
Head circumference[a] (cm)	32.4±2	(23–37)	33.6±2	(25–39.5)	15.8	0.0001
Apgar — 1 min (cm)	8.0±1	(1–9)	8.0±2	(1–9)	−0.37	0.70
Apgar — 5 min	8.8±6	(5–9)	8.8±0.6	(5–9)	0.30	0.77
Hobel risk score	6.0±14	(0–85)	4.1±11	(0–65)	−1.4	0.17
Female	82 (52%)		80 (50%)		0.16	0.70
SGA[b]	19 (12%)		2 (1%)		18.1	0.001
Microcephaly	40 (26%)		14 (9%)		15.9	0.001
Non-maternal care	45 (29%)		1 (<1%)		50.1	0.001

[a] p adjusted for gestational age.
[b] Small for gestational age.

Table 5 gives the results of the maternal postpartum interview of drug use for the 319 women whose infants received the NB Assessment. The majority (97%) of cocaine users used the "crack" form of the drug. For all trimesters, heavy cocaine-using women used alcohol, marijuana, and tobacco more frequently and in higher amounts than non-cocaine users with the exception of frequency of alcohol use during the month prior to pregnancy. Heavy cocaine users also had more drinks per occasion in trimesters 1 and 3 than light users and smoked more joints per occasion in trimesters 2 and 3. The number of cocaine "rocks" consumed, but not the frequency of use, was different for heavy vs.

Table 3
Sample characteristics

Maternal	Cocaine: Heavy (n=82) M±SD	Heavy Range	Light (n=76) M±SD	Light Range	Non-cocaine (n=161) M±SD	Non-cocaine Range	F/χ^{2a}	p
Age (years)	29.0±5	(18–41)	28.7±5	(18–38)	25.6±5	(18–40)	18.8	0.0001[b]
Parity	3.4±2	(1–10)	3.2±2	(1–8)	2.7±2	(1–10)	3.4	0.03[c]
Gravida	4.8±2	(1–14)	4.6±2	(1–11)	3.7±2	(1–11)	8.5	0.0002[b]
Number of prenatal care visits[d]	5.5±5	(0–25)	6.2±5	(0–23)	8.7±5	(0–25)	15.6	0.0001[b]
Month began prenatal care	4.8±2	(1–9)	4.2±2	(1–9)	3.5±2	(1–9)	12.9	0.0001[b]
PPVT-R standard score	73.3±13	(41–104)	74.2±15	(40–121)	78.6±15	(41–123)	4.3	0.02[c]
WAIS-R BD score	7±2	(1–14)	6.9±2	(1–11)	7.3±2	(1–13)	1.2	0.29
WAIS-R PC score	6.5±2	(3–12)	6.6±2	(3–11)	7.0±2	(2–17)	1.8	0.17
General severity index (mother)	0.96±0.9	(0–3.8)	0.66±0.6	(0–3.4)	0.47±0.5	(0–2.9)	15.8	0.0001[e]
General severity index (current caregiver)	0.72±0.7	(0–3.8)	0.56±0.5	(0–2.7)	0.47±0.5	(0–2.9)	4.22	0.02[c]
Race (non-white)	68 (83%)		60 (79%)		129 (80%)		0.20	0.65
No prenatal care	14 (17%)		10 (13%)		15 (9%)		13.1	0.08
Alcohol use	68 (84%)		66 (92%)		101 (63%)		17.3	0.001[b]
Marijuana use	45 (56%)		38 (53%)		18 (11%)		57.3	0.001[b]
Tobacco use	74 (91%)		62 (86%)		65 (40%)		70.8	0.001[b]
Amphetamine use	2 (3%)		2 (3%)		2 (1%)		0.6	0.46
Barbiturate use	1 (1%)		1 (1%)		1 (1%)		0.3	0.60
Valium use	9 (15%)		11 (18%)		0 (0%)			0.000[b,f]
Heroin use	3 (4%)		1 (1%)		0 (0%)			0.03[c,f]
PCP use	3 (4%)		5 (7%)		0 (0%)			0.000[b,f]
Maternal employment	6 (7%)		3 (4%)		34 (21%)		11.6	0.001[b]
Married	6 (7%)		4 (5%)		30 (19%)		8.1	0.004[b]
Socioeconomic status (IV/V)	81 (99%)		72 (96%)		157 (98%)		0.2	0.66
Education (<high school graduate)	33 (40%)		35 (46%)		53 (33%)		1.9	0.17

[a] Mantel–Haenszel chi-square.
[b] None/light and heavy.
[c] None/heavy.
[d] p adjusted for gestational age.
[e] None<light<heavy.
[f] Fisher's exact test.

Table 4
Sample characteristics

	Cocaine				Non-cocaine			
	Heavy (n=82)		Light (n=76)		(n=161)			
Infant	M±SD	Range	M±SD	Range	M±SD	Range	F/χ^{2a}	p
Birthweight (g)[b]	2723±587	(905–3905)	2743±701	(930–3995)	3112±629	(1017–4515)	163.2	0.0001[c]
Gestational age (weeks)	37.9±3	(29–42)	37.6±3	(28–42)	38.7±2	(30–42)	5.5	0.005[c]
Birth length (cm)[b]	47.4±4	(34.5–55)	47.4±4	(34–58)	49.3±3	(37–57)	107.8	0.0001[c]
Head circumference (cm)[b]	32.4±2	(24.5–36)	32.3±3	(23–37)	33.6±2	(25–39.5)	101.48	0.0001[c]
Apgar — 1 min	8.1±1	(1–9)	8.0±2	(2–9)	8.0±2	(1–9)	0.30	0.74
Apgar — 5 min	8.8±0.5	(6–9)	8.8±0.7	(5–9)	8.8±0.6	(5–9)	0.45	0.63
Hobel score	5.2±13		6.9±15		4.1±11		1.31	0.27
Female	42 (51%)		40 (53%)		80 (50%)		0.08	0.77
SGA[d]	10 (12%)		9 (12%)		2 (1%)		0.14	0.001[c]
Microcephaly	19 (25%)		21 (28%)		14 (9%)		10.8	0.001[c]
Non-maternal care	30 (37%)		15 (20%)		1 (<1%)		59.2	0.001[e]

[a] Mantel–Haenszel chi-square.
[b] p adjusted for gestational age.
[c] None < or > light and heavy.
[d] Small for gestational age.
[e] None<light<heavy.

light users. Table 6 shows the summary measures of frequency and severity of drug use for alcohol, marijuana, tobacco, and cocaine for cocaine-using and cocaine-negative women during the month prior to and during the trimesters of pregnancy.

For each group, comparisons were made between those infants who were administered the NB Assessment and the remainder of the sample. Non-exposed infants were more likely to receive the NB Assessment compared to exposed infants (82% non-exposed, 161/197; 73% exposed, 158/215; $p<0.05$). Cocaine-exposed infants seen for neurobehavioral exams vs. those who did not receive it had mothers who were younger ($p<0.001$), with fewer children ($p<0.001$), and more prenatal care visits ($p<0.0001$), but did not differ on any birth parameter, or on Apgar score, gender, race, maternal socioeconomic or marital status. Within the non-exposed group, infants who received the exam compared to those who did not were more likely to have received prenatal care ($p<0.10$), and to be of higher gestational age ($p<0.06$) due to a few very premature infants who were too ill to participate, but did not differ on any other variable.

2.1.1. Neurobehavioral outcomes

Infants were seen for follow-up at mean chronologic ages of 4.0±3 and 4.7±3 weeks ($t=-2.7$, $p<0.035$), corrected ages for prematurity of 2.7±2 and 2.5±3 weeks ($t=-0.1$, $p<0.34$) for the non-exposed and exposed groups, respectively. When only exposed and non-exposed groups were compared, there were cocaine effects on the NB items indicating more abnormalities in movement and tone ($F=4.9$, $p<0.026$), and a trend for jitteriness ($F=3.1$, $p<0.08$). However, when the cocaine-exposed group was categorized based on heavy vs. light exposure status, the differences became more pronounced (see Table 7). Heavily exposed infants had significantly more attentional abnormalities and jitteriness than the lightly exposed and non-exposed groups which, on all parameters, did not differ. Heavily exposed infants were more likely to be identified with any abnormality than non-exposed infants, and there was a trend for heavily exposed infants to be more likely to be identified with any abnormality than lightly exposed infants. Heavily exposed infants also had more movement and tone abnormalities and sensory asymmetries than non-exposed infants. There were significant ($p<0.05$) gestational age effects for sensory asymmetry, movement/tone, and head control with more abnormal scores associated with lower gestational age at birth, but these effects did not reduce the relationship of heavy cocaine exposure level to abnormal outcomes.

Infants were compared across groups to determine if there was a relationship of cocaine exposure to infant testability. There was a trend for the three groups to differ in the percentage of infants who came for the exam but were not testable because they were too sleepy or fussy (24 (13%), 18 (19%), and 22 (21%) for none, lightly, and heavily exposed groups, respectively; Mantel–Haenszel $\chi^2=3.6$, $p<0.056$). Follow-up tests indicated a trend for heavily exposed infants to be more likely than non-exposed infants to be untestable ($\chi^2=3.5$, $p<0.06$).

2.2. Maternal self-report of drug use and neurobehavioral outcomes

Table 8 presents correlations of maternal self-report of severity and frequency of cigarette, alcohol, marijuana, and cocaine use by trimester with neurobehavioral outcomes which had shown differences between the heavily

Table 5
Frequencies and amounts of prenatal drug use by group

	Cocaine		Non-cocaine	
	Heavy (n=82)	Light (n=76)	(n=161)	F*
Cigarettes/day				
Month prior	15.4±13	11.4±10	5.5±10	23.9[a,b]
Trimester 1	14.6±13	9.5±8	4.3±9	29.4[c]
Trimester 2	12.1±12	8.3±8	3.3±8	27.7[c]
Trimester 3	10.6±12	7.6±7	3.0±7	22.8[a,b]
Alcohol drinks/day				
Month prior	4.6±7	3.1±3	1.1±2	23.3[a,b]
Trimester 1	4.3±6	2.4±3	0.6±1	30.1[c]
Trimester 2	2.8±5	1.6±3	0.3±1	20.5[c]
Trimester 3	2.4±5	1.3±2	0.3±1	16.4[c]
Alcohol days/week				
Month prior	2.1±2	2.7±2	1.5±2	7.7[b]
Trimester 1	2.2±2	2.3±2	0.9±2	18.8[a,b]
Trimester 2	1.5±2	1.7±2	0.5±2	25.8[a,b]
Trimester 3	2.0±2	1.8±3	0.7±2	11.9[a,b]
Marijuana joints/day				
Month prior	0.9±2	2.6±1	1.3±2	4.1[a]
Trimester 1	0.8±2	0.5±2	0.1±1	8.9[a]
Trimester 2	0.7±1	0.3±1	0.6±0.4	15.4[a,d]
Trimester 3	0.5±1	0.2±1	0.04±0.2	15.1[a,d]
Marijuana days/week				
Month prior	1.6±2	1.3±2	0.3±1	19.4[a,b]
Trimester 1	1.4±2	1.6±2	0.2±1	15.7[a,b]
Trimester 2	1.1±2	0.6±2	0.1±1	15.2[a,b]
Trimester 3	1.0±2	0.8±2	0.1±1	11.9[a,b]
	Cocaine			
	Heavy (n=82)	Light (n=76)	t	p
Cocaine rocks/day				
Month prior	7.8±11	1.9±2	−4.5	0.0001
Trimester 1	8.1±13	1.8±4	−4.1	0.0001
Trimester 2	6.6±11	1.2±2	−3.9	0.0001
Trimester 3	4.3±7	0.9±1	−4.0	0.0001
Cocaine days/week				
Month prior	2.0±2	2.0±2	−0.02	0.99
Trimester 1	1.7±2	1.8±2	0.14	0.89
Trimester 2	1.8±2	1.6±2	−0.81	0.41
Trimester 3	2.4±2	2.2±2	−0.55	0.58

* All comparisons are significant at the <0.05 level.
[a] Non-cocaine<heavy.
[b] Non-cocaine<light.
[c] Non-cocaine<light<heavy.
[d] Light<heavy.

exposed and lightly and non-exposed groups. Jitteriness was related to the number of cigarettes smoked for the month prior and all trimesters of pregnancy, to level of third trimester alcohol use, and to trimesters 2, 3, and average cocaine use. A similar pattern was found for movement/tone abnormalities which were positively related to cigarette exposure for all time points, as well as to trimesters 2, 3, and average cocaine use. In contrast, positive correlations were found for attentional abnormalities with trimesters 1, 2 and average marijuana exposure; with the month prior alcohol exposure; and with a trend for a relationship to average cocaine exposure. Sensory asymmetry was related to average marijuana exposure with a trend for a relationship with month prior to and average cocaine exposure. There was no relationship of PCP, heroin, barbiturates, methamphetamine, or benzodiazepine use to any outcome.

2.3. Meconium assays and outcomes

Table 9 presents the concentration (ng/g) of each of the cocaine and marijuana metabolites measured by group for those infants with meconium analyses. As noted in Table 10, the likelihood of having any abnormality on the NB assessment and jitteriness were positively related to the amount of all four cocaine metabolites assayed. Movement and tone abnormalities were positively related to the concentration of cocaine, cocaethylene, and BZE. Attentional abnormalities were related to higher amounts of cocaethylene. Sensory and motor asymmetries were unrelated to the quantity of any metabolite. The amount of THC in meconium was also unrelated to any outcome.

2.4. Confounding and mediating variables

A number of confounders were also related to neurobehavioral outcomes. Attentional abnormalities were associated with fewer prenatal visits, r (306)=−0.12, p<0.05; maternal GSI score, r (304)=0.19, p<0.001; and current caregiver GSI score, r (298)=0.13, p<0.02. Movement and tone abnormalities were related to fewer prenatal visits, r (304)=−0.14, p<0.05 and higher parity, r (306)=0.11, p<0.07; jitteriness was related to lower maternal BD score, r (295)=−0.13, p<0.03; higher parity, r (297)=−0.10, p<0.08 and fewer prenatal visits, r (297)=−12, p<0.04; and sensory asymmetry was related to maternal GSI score, r (304)=0.17, p<0.01 and current caregiver GSI score, r=(296)=0.11, p<0.07. Higher likelihood of any abnormality was related to fewer prenatal visits, r (317)=−0.12, p<0.03; marital status, r=−0.09, p<0.10 social class, r (318)=−0.10, p<0.09; and maternal GSI, r (306)=0.09, p<0.10. Chronological age was unrelated to outcomes, with the exception of state abnormalities which were not affected by exposure status. Older chronological age was related to fewer state abnormalities. There were no examiner effects on any of the outcomes differentiated by severity of cocaine exposure, and there were no differences between the light and heavy groups on any of the potential confounders, except for maternal GSI score.

A number of potential mediators of cocaine effects were also identified, i.e. for movement and tone: GA, r (306)=−0.16, p<0.006; birthweight, r (306)=−0.18, p<0.002; length, r (306)=−0.11, p<0.006; head circumference, r (306)=−0.13, p<0.02 and Hobel risk score, r (304)=0.17, p<0.01; and for jitteriness: birthweight, r

Table 6
Summary measures of tobacco, alcohol, marijuana, and cocaine by trimester

	Cocaine		Non-cocaine		
	Heavy (n=82)	Light (n=76)	(n=161)	F/t	p
Number of cigarettes/day	13.2±12	9.2±8	4.0±8	29.4	0.0001[a]
Alcohol use[b]					
Month prior	18.1±31	10.3±16	2.1±6	22.3	0.0001[a]
Trimester 1	16.6±29	7.9±13	1.2±4	24.5	0.0001[a]
Trimester 2	10.9±25	4.3±10	0.6±3	15.2	0.0001[c,d]
Trimester 3	7.8±20	3.3±9	1.2±8	7.7	0.0005[c]
Average	13.3±22	6.5±10	1.3±5	24.9	0.0001[a]
Marijuana use[b]					
Month prior	2.3±5	1.4±3	1.6±10	0.31	0.73
Trimester 1	2.3±5	1.0±3	0.6±4	4.6	0.01[c]
Trimester 2	2.4±6	0.5±2	0.2±2	11.7	0.0001[c,d]
Trimester 3	1.8±5	0.4±2	0.1±1	8.9	0.002[c,d]
Average	2.2±5	0.8±2	0.6±4	5.1	0.006[c]
Cocaine use[b]					
Month prior	44.6±65	8.3±9		−4.8	0.0001
Trimester 1	53.6±82	7.8±7		−4.8	0.0001
Trimester 2	40.0±78	4.6±6		−3.9	0.0001
Trimester 3	18.2±34	2.5±4		−3.9	0.0001
Average	38.4±51	6.3±5		−5.4	0.0001

[a] None/light/heavy.
[b] Number of drinks, joints or "rocks"/day × number of days/week.
[c] None/heavy.
[d] Light/heavy.

(299)=−0.11, p<0.06. For any abnormality: birthweight, r (316)=−0.13, p<0.03; birth length, r (316)=−0.10, p<0.08; GA, r (316)=−0.11, p<0.05 were related.

Because maternal demographic factors and infant birth outcomes were not different between heavy and light cocaine groups, the pattern of differences in specific neurobehavioral outcomes could not be attributed to these confounders or potential mediators with the exception of maternal GSI and current caregiver GSI. These two variables were highly correlated since the majority of infants remained with their biological mothers. Because — for the three outcomes for which there was a relationship (p<0.10) with GSI score — the stronger relationship was always that of the biologic mother, maternal GSI was assessed, along with confounding drug variables, in logistic regression models.

Table 7
Abnormalities on neurobehavioral assessment

	Cocaine		Non-cocaine		
	Heavy (n=82)	Light (n=76)	(n=161)	F/χ^{2a}	p
Chronological age	4.8±3	4.6±3	4.0±3	2.4	0.10
Corrected age	2.7±2	2.2±2	2.7±2	1.4	0.24
Attention	8 (10%)	2 (3%)	5 (3%)	4.3	0.04[b]
Sensory asymmetry	6 (8%)	2 (3%)	3 (2%)	4.4	0.04[c]
Head control	10 (13%)	3 (4%)	14 (9%)	0.4	0.55
Movement and tone	21 (26%)	12 (16%)	18 (12%)	7.4	0.01[c]
Motor asymmetry	3 (4%)	1 (1%)	8 (5%)	0.6	0.45
State	3 (4%)	2 (3%)	11 (7%)	1.6	0.20
Jitteriness	19 (24%)	8 (11%)	15 (10%)	7.7	0.01[b]
Any abnormality	39 (48%)	21 (28%)	49 (30%)	5.7	0.02[c,d]

[a] Mantel–Haenszel chi-square.
[b] Heavy > none and light, p<0.05.
[c] Heavy > none, p<0.05.
[d] Heavy > light, p<0.10.

Table 8
Spearman correlations of neurobehavioral subscale scores with maternal self-report of drug use

	Attention	Sensory asymmetry	Movement/ Tone	Jitteriness	Any abnormality
Number of cigarettes/day					
Month prior	0.08	0.07	0.14**	0.13**	0.05
Trimester 1	0.07	0.09	0.15***	0.11*	0.07
Trimester 2	0.01	0.04	0.15***	0.12**	0.05
Trimester 3	0.02	0.04	0.15***	0.13**	0.04
Average	0.06	0.07	0.15**	0.13**	0.06
Alcohol[a]					
Month prior	0.11*	0.05	0.09	0.07	0.01
Trimester 1	0.09	0.05	0.08	0.06	0.02
Trimester 2	0.06	0.01	0.06	0.05	−0.01
Trimester 3	0.06	0.05	0.07	0.11**	0.06
Average	0.09	0.06	0.05	0.06	−0.02
Marijuana[a]					
Month prior	0.07	0.09	−0.03	0.06	−0.02
Trimester 1	0.11**	0.07	−0.02	0.00	−0.04
Trimester 2	0.12**	0.04	0.02	0.07	0.00
Trimester 3	0.07	0.04	0.04	0.04	0.02
Average	0.10*	0.12**	−0.02	0.04	−0.04
Cocaine[a]					
Month prior	0.08	0.09*	0.07	0.05	0.06
Trimester 1	0.08	0.08	0.06	0.04	0.03
Trimester 2	0.00	−0.05	0.18***	0.13**	0.08
Trimester 3	0.08	0.02	0.14**	0.12**	0.07
Average	0.10*	0.11*	0.13**	0.11*	0.08

* $p<0.10$.
** $p<0.05$.
*** $p<0.01$.
[a] Number of drinks, joints or "rocks"/day × number of days/week.

2.4.1. Results of logistic regressions

When logistic regressions were calculated to control for confounding drug variables and maternal GSI, few and weak independent relationships between individual drug use and specific outcomes were found. As noted previously, logistic regressions were based on the comparisons in Table 7. For those comparisons in which heavily exposed infants (i.e. attention, jitteriness) differed from both lightly and non-exposed infants, only drug confounders and maternal GSI scores were controlled in the regression, since there were no differences between heavy and light exposure groups on other confounding variables. For those comparisons in which differences were found only for heavy exposure in comparison to non-exposure (sensory asymmetry, movement/tone, and any abnormality), all variables related to outcome were controlled. The final steps of the regression models are found in Table 11. The likelihood of having any abnormality noted, adjusted for confounders, was higher for the heavily exposed infants compared to lightly exposed and non-exposed infants, and these cocaine effects were not mediated by maternal distress or any birth outcome. Heavy cocaine exposure significantly predicted jitteriness, after control for cigarette and alcohol exposure, and was not mediated by any birth outcome. There was a trend for heavy cocaine exposure to predict sensory asymmetry (OR=3.10, $p<0.08$), but this effect was mediated or confounded by maternal GSI score. There was also a trend for cigarette use averaged over the pregnancy to predict movement/tone abnormalities after control for heavy cocaine exposure. There were no independent effects of any single drug on attention, but a significant effect of maternal psychological distress after accounting for the effects of alcohol, marijuana, and cocaine, indicating that maternal psychological distress mediated or confounded the zero-order relationships between these drugs and attentional abnormalities.

2.5. Discussion

The present study corroborates previous findings of early neurobehavioral abnormalities in cocaine-exposed infants using a large prospective sample with quantification of level of exposure through both biologic and self-report measures as well as control for a large number of confounding variables, including maternal psychological distress and IQ, level of prenatal care, and non-maternal caregiver characteristics, which have not been previously considered.

Infant behavior was negatively affected by cocaine exposure as well as other factors. Heavy cocaine exposure, compared to light and non-exposure, was associated with almost a doubling of risk for detection of any abnormality. Controlling for all other factors, heavily cocaine-exposed infants were more than four times as likely to be jittery than

Table 9
Concentration (ng/g) of cocaine and marijuana metabolites in meconium

	Cocaine				Non-cocaine	
	Heavy (n=69)		Light (n=49)		(n=150)	
	M±SD	Range	M±SD	Range	M±SD	Range
Metabolite						
Cocaine	183 ± 383	(0–2271)	0.61 ± 3	(0–14)	–	
Cocaethylene	37 ± 87	(0–417)	0.86 ± 4	(0–25)	–	
Benzoylecgonine	377 ± 1293	(0–7088)	8.7 ± 26	(0–152)	–	
m-OH-BZE	541 ± 1708	(0–9998)	6.8 ± 15	(0–53)	–	
Tetrahydracannabinol	1.5 ± 7	(0–48)	4.9 ± 21	(0–123)	3.5 ± 19	(0–148)

Table 10
Spearman correlations of quantity of cocaine metabolites in meconium with neurobehavioral abnormalities (n=268)

	Cocaine (ng/g)	Cocaethylene (ng/g)	Benzoylecgonine (ng/g)	m-OH-BZE (ng/g)
Attention	0.08	0.24****	0.10	0.10
Sensory asymmetry	0.02	0.09	0.04	0.05
Movement and tone	0.18***	0.14**	0.14**	0.06
Jitteriness	0.19***	0.20***	0.20***	0.15**
Any abnormality	0.21****	0.13**	0.16***	0.10*

* $p<0.10$.
** $p<0.05$.
*** $p<0.01$.
**** $p<0.001$.

lightly and non-exposed infants. Jitteriness has been reported in prior clinical descriptions of cocaine-exposed infants [8,20,38], but has not been documented in a large sample, after acute drug effects have diminished. Maternal report of severity of third trimester alcohol use, second and third trimester cocaine use, and the amount of the cocaine metabolite cocaethylene, which results from the combined use of cocaine and alcohol, were also correlated with infant jitteriness. Since previous studies have found tremors in alcohol-exposed infants [29] in the neonatal period, and since the majority of cocaine-exposed infants were also alcohol-exposed, it is likely that jitteriness was a result of polydrug exposure, although independent effects of cocaine were found. Fetal exposure to alcohol and cocaine simultaneously has been hypothesized to produce synergistic effects on cocaine's actions at the dopamine transport site [43].

Sensory asymmetries using the NB Assessment have been found to be more prevalent in infants with known neurologic impairment [20], suggesting greater developmental risk for the heavily exposed group.

Cocaine, alcohol, and marijuana exposures were all related to attentional abnormalities, but no single drug predicted outcome independently. Similarly, in a study by Coles et al. [12], the amount of prenatal marijuana exposure was related to poorer orientation on the BNBAS at 14 days in a sample of full-term infants, and the combination of marijuana and tobacco was related to decreased alert responsiveness in the immediate neonatal period in the study of Eyler et al. [16]. Mirochnick et al. [37] found maternal marijuana and cocaine use during pregnancy to be associated with increased plasma norepinephrine concentrations which were associated with poorer NBNAS orientation scores in the first 2 days of life but not at later ages.

Severity of alcohol exposure in the month prior to pregnancy as well the concentration of the metabolite cocaethylene, formed from the combination of cocaine and alcohol, were also related to the attentional abnormalities, in this sample, while the three other cocaine metabolites were unrelated. Both alcohol and cocaine exposures have been related to visual attentional problems in prior studies [7,16,34,38,53,61] which involved cocaine/polydrug-exposed infants with both alcohol and marijuana exposure. These findings are consistent with the theory that cocaine has effects on the developing brain involving the dopamine system, with particular effects on arousal and attentional capacities [26,33,60]. The relationship of the concentration of cocaethylene to attentional abnormalities supports the hypothesis that the presence of multiple drugs may have synergistic effects on early brain functions [43,55]. Our results also concur with findings of poorer

Table 11
Logistic regressions predicting abnormal neurobehavioral outcomes

Predictors	Odds ratio	95% Confidence interval	p
Outcome: attention			
Alcohol month prior	1.20	(0.82, 1.8)	0.34
Marijuana trimester 2	1.29	(0.71, 2.3)	0.40
Cocaine — heavy vs. light and none	2.02	(0.55, 7.4)	0.29
Maternal GSI	4.41	(1.02, 18.9)	0.05
Outcome: sensory asymmetry			
Marijuana average	1.30	(0.62, 2.7)	0.39
Cocaine — heavy vs. none	2.41	(0.51, 11.5)	0.27
Maternal GSI	4.92	(0.87, 27.9)	0.07
Outcome: movement/tone			
Number of prenatal visits	0.96	(0.89, 1.0)	0.36
Parity	1.13	(0.94, 1.4)	0.18
Cigarettes average	1.32	(0.96, 1.8)	0.09
Cocaine — heavy vs. none	1.50	(0.66, 3.5)	0.34
Outcome: jitteriness			
Cigarettes average	1.34	(0.88, 1.6)	0.25
Alcohol — trimester 3	0.05	(0.71, 1.3)	0.81
Cocaine — heavy vs. light and none	4.31	(1.05, 5.0)	0.04
Outcome: any abnormality			
Number of prenatal visits	0.97	(0.93, 1.0)	0.29
Marital status	1.24	(1.0, 1.6)	0.05
Socioeconomic status	1.24	(0.07, 1.4)	0.12
Cocaine — heavy vs. light and none	1.88	(1.1, 3.4)	0.03
Maternal GSI	1.27	(0.60, 2.7)	0.54

visual recognition memory in heavily cocaine-exposed infants at older ages [25,61].

Heavily cocaine-exposed infants had more movement/tone abnormalities than non-exposed infants, consistent with prior smaller, less well-controlled studies which found cocaine exposure to be related to motor and reflex abnormalities in the neonatal period [6,7,12,46,62] and to motor deficits at later ages [1,2,54]. These effects were not significant after control for cigarette exposure, however, which had independent effects. Coles et al. [12] found duration and amount of cigarette use during pregnancy independently related to abnormal reflexes, but these effects did not persist past 2 days postpartum. Nicotine, the primary drug found in tobacco, may have direct and indirect effects on fetal development similar to cocaine. Like cocaine, nicotine reduces blood flow to the fetus and may induce fetal hypoxia [11]. Nicotine may also directly affect fetal brain development in a manner similar to cocaine [58]. In the present study, heavy cocaine exposure and heavy tobacco exposure were confounded. Since the study was designed to assess cocaine effects, findings related to nicotine or other drug effects should be interpreted cautiously.

The concentration of cocaine metabolites measured in meconium was related to all but one, of the observed infant neurobehavioral effects, consistent with several studies which related level of metabolites in meconium samples to neonatal behavioral outcomes [13,53,63]. The present findings thus provide additional support for the quantification of cocaine metabolites as a useful indicator of level of fetal cocaine exposure.

Of particular interest is the potentially mediating role of maternal psychological distress in the relationship of drug exposure to attentional abnormalities and sensory asymmetry. Maternal psychological distress symptoms have been related to poorer neurobehavioral outcomes in healthy, non-substance-exposed neonates [17,71], and to long-term cognitive outcomes in both substance-exposed [24,54] and non-exposed populations [51]. Moreover, non-human primate offspring of mothers exposed to stress or stress hormones fetally have higher incidences of neuromotor deficits, hypotonia and attentional disorders in the postpartum period [10,48], as well as manifest alterations in concentrations of dopamine and norepinephrine in cerebral spinal fluid [49]. In other non-human primate studies, adverse neurobehavioral and fetal growth effects of fetal alcohol exposure were exacerbated by prenatal stress [50]. In the present study, the strongest relationships with aberrant neurobehavioral functioning were found with biologic maternal distress rather than current caregiver distress.

Substance-abusing women have high rates of comorbid psychological disorders, especially depressive and anxiety symptoms, which may be predisposing stress factors for, as well as effects of, chronic substance abuse [27,35,56]. Such disorders may have additive or synergistic effects on long-term developmental outcomes of drug-exposed infants [21,24,54]. Generally, maternal psychopathology has been conceptualized as affecting child outcomes primarily through maternal caregiving interactions with her infant [17,36,51,54]. The present findings, along with work which documents early neurobehavioral and biochemical changes in human and non-human primate neonates whose mothers experienced psychological stress during pregnancy [10,17,48–50,70], suggest an additional path in which maternal prenatal psychological distress affects fetal biochemistry and neonatal neurobehavior. Our data suggest that the infants of substance-using women with concomitant psychological disorders may be at greater biologic as well as psychological risk. Because, in this sample, biologic maternal psychological distress was highly correlated with current caregiver distress, as most infants remained in the care of their biologic mothers, the present study could not determine whether negative effects were related directly to prenatal stress or to the caregiving environment. In all cases, however, the correlation of biological maternal distress to outcomes was stronger than that of the current caregiver's distress.

The present study has several advantages which may have increased the likelihood of detecting significant drug effects. Maternal drug status was determined through both biologic measures (meconium and urine screen) and clinical interview, possibly enhancing reliability of classification [3,71]. Moreover, cigarette, alcohol, and marijuana use were quantified, reducing the likelihood that the effects of other drugs were undercontrolled and that the observed effects are actually due to other drugs. All infants were also examined when any drug, including obstetric drugs, would have cleared the infant's system; thus, the findings are not due to acute or withdrawal effects.

Some limitations to the present study should be considered. Although examiners were masked to infant cocaine exposure status, it may have been possible to identify drug exposure through maternal or caregiver behaviors or characteristics since all infants were assessed with the caregiver present. There was little likelihood, however, that examiners were aware of whether mothers were light or heavy users, since infant birth and demographic characteristics were not different between these groups.

Another concern is that the drug assessments were conducted retrospectively, making reliability of report problematic. However, in previous findings from this cohort, maternal self-report of severity of cocaine use was significantly related to quantity of cocaine metabolites in meconium [3], suggesting that careful interviewing in a non-judgmental setting can yield data adequately sensitive to the detection of drug effects. The classification of cocaine users into heavy and light groups may also have been more reliable due to the use of both biologic and self-report data. Both meconium analyses and maternal self-report, however, have limitations in establishing reliability of a woman's drug use history. The illegal status of cocaine may lead respondents to deny or minimize the extent of use in clinical interviews. Meconium analyses do not detect first trimester

drug use and contamination from infant urine is likely, compromising reliability and validity.

In another study [3] of this cohort, we demonstrated that a significant percentage of infants from the heavy group would have been classified as lightly exposed if only maternal self-report measures were used. Since all the neurobehavioral effects were found only with heavy exposure, they may not have been detected if heavily exposed infants had been misclassified as lightly exposed, resulting in a significant loss of power in the heavy group [52]. The use of quantification of meconium in combination with self-report measures may significantly enhance reliability and thus, sensitivity to threshold effects of drugs.

A further caveat is that although with statistical control for other drug exposures two independent effects of cocaine were found, it is not possible to attribute negative effects solely to cocaine. In this sample, all cocaine-exposed infants were polydrug-exposed. While some infants in the control group were exposed only to cigarettes, alcohol, or marijuana, no infant in the cocaine group was exposed only to cocaine.

In summary, heavy cocaine exposure, in comparison to light and non-exposure, was associated with more aberrant infant neurobehavioral functioning in the late neonatal period, but the only specific abnormality which could be independently linked to cocaine was jitteriness. Longitudinal investigations of the outcomes of cocaine-exposed cohorts are needed to determine if these early differences persist and relate to poorer functional long-term outcomes.

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