

Adverse Effects of Fetal Cocaine Exposure on Neonatal Auditory Information Processing

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ABSTRACT. *Background.* Studies with animals have shown that in utero exposure to cocaine interferes with fetal brain development by disrupting the processes of neuronal proliferation, differentiation, and migration, often leading to subsequent neurobehavioral deficits. However, studies with humans have produced inconsistent findings. Although neurobehavioral abnormalities have been observed among cocaine-exposed infants in several studies and in some cases dose-response effects have been found, the specific neurobehaviors affected vary from one study to the next. Researchers studying the effects of fetal cocaine-exposure are faced with many difficult challenges. For example, women who use cocaine typically use other substances in addition to cocaine, many of the methods available for identifying cocaine-exposed neonates are not reliable, and the available methods for assessing cocaine-exposed newborns may not be sufficiently sensitive to detect the subtle effects of cocaine on the developing central nervous system. Despite these difficulties, there is a growing body of research that suggests that fetal cocaine exposure is associated with subsequent language deficits among children exposed in utero. However, it is virtually impossible to disentangle the effects of the impoverished environments in which these children are often raised from the effect, if any, of fetal cocaine exposure. To determine the effects of fetal cocaine exposure independent of postnatal environmental effects, cocaine-exposed neonates would ideally be tested within the first few weeks of birth, and to identify early risks for subsequent language delay, well-researched auditory information processing measures could be used.

Objective. The purpose of the present study was to assess the effects of fetal cocaine exposure on neonatal auditory information processing ability. To overcome limitations of some previous studies on the neuroteratogenic effects of cocaine, such as unreliable subject identification techniques, inadequate control over confounding variables, and questionable measures of central nervous system integrity, a valid measure of auditory information processing was used in a rigorous, case-control design.

Method. Newborn information processing was assessed using habituation and recovery of head-turning toward an auditory stimulus across the 3 phases of the

procedure: familiarization, novelty, and dishabituation. During the familiarization phase, the infant orients and habituates to a repeated word; during the novelty phase, the infant recovers head-turning to a novel word and subsequently habituates to this word; and during the dishabituation phase the infant displays renewed head-turning to the return of the original stimulus. Testing takes ~20 minutes. This procedure has been shown previously to discriminate among infants at high-, moderate-, and low-risk for subsequent developmental delay. Twenty-five cocaine-exposed and 25 nonexposed control neonates, identified by meconium analysis, urine analysis, and/or maternal self-report, were tested on the auditory information processing procedure. The majority of infants were tested within the first few days of birth. Cocaine-exposed and control neonates were matched on birth weight, gestational age, Apgar scores, age at testing, and socioeconomic status as reflected by household income. Mothers were matched on age, weight gain, cigarette smoking, and alcohol consumption.

Results. Fetal cocaine exposure was associated with impaired auditory information processing. Both cocaine-exposed and nonexposed control neonates oriented to the familiarization stimulus, but cocaine-exposed neonates displayed impaired habituation. Moreover, cocaine-exposed neonates did not recover or habituate to the novel stimulus or dishabituate to the return of the familiarization stimulus. Whereas nonexposed, control infants exhibited high levels of turning away from the familiarization stimulus during habituation (implying boredom), followed by high levels of turning toward the novel stimulus, indicating recovery of attention, the cocaine-exposed infants turned randomly. Clearly, auditory information processing of cocaine-exposed infants was impaired, despite the fact that they exhibited the same overall number of head-turns and the same high level of positive state as the nonexposed infants.

Conclusions. The results imply that cocaine is a neuroteratogenic agent that impairs auditory information processing ability during the newborn period. Cocaine-exposed neonates exhibited a response pattern that is consistent with slower speed of auditory information processing. These deficits were observed within the first few days of birth, before adverse postnatal environmental influences could exert their effect. Moreover, the case-control design increased the probability that the observed information processing deficits were due primarily to the direct effects of fetal exposure to cocaine and not other prenatal factors. However, the long-term implications of these findings for the development of the infant/child are not known and must be addressed in follow-up studies. *Pediatrics* 2000; 105(3). URL: <http://www.pediatrics.org/cgi/content/full/105/3/e40>; cocaine, neonate, information processing, habituation, novelty responsiveness.

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ABBREVIATIONS. CNS, central nervous system; NBAS, Neonatal Behavioral Assessment Scale; BW, birth weight; GA, gestational age; FTII, Fagan Test of Infant Intelligence; SES, socioeconomic status as reflected by household income; WG, mother's pregnancy weight gain; CARE, extent of prenatal care; BE, benzoylcegonine.

The number of pregnancies complicated by maternal use of cocaine increased dramatically during the 1980s and early 1990s.¹ Although estimates of the number of newborns exposed to cocaine prenatally in the United States vary widely depending on the geographical region sampled and the screening methods used, prevalence rates range from ~1% in suburban and rural areas^{2,3} to >30% in some urban areas,⁴ with a nationwide average in the order of 10%. Canadian prevalence rates are similar, with 3% of neonates testing positive for prenatal cocaine exposure in suburban Toronto and 12.5% in urban Toronto.⁵ Cocaine can penetrate the placenta and accumulate in the fetal brain at concentrations up to 4 times greater than those observed in plasma.⁶ Furthermore, prenatal cocaine-exposure has been shown by animal studies to disrupt fetal central nervous system (CNS) development by interfering with the processes of neuronal proliferation, migration, and differentiation.⁷⁻⁹ Fetal cocaine-exposure also leads to significant alterations in brain activity among laboratory animals^{10,11} and there is an emerging consensus among some researchers that fetal cocaine exposure in humans may lead to subtle but significant deficits in children, particularly with behaviors necessary for academic success.¹² However, the effects of fetal cocaine-exposure on the development of the CNS in human infants are not clear and many studies to date have been subject to a variety of methodologic limitations.

In early studies using the Neonatal Behavioral Assessment Scale (NBAS),¹³ cocaine-exposed infants exhibited a variety of neurobehavioral impairments relative to control infants. However, the specific NBAS cluster scores affected differed across studies. This lack of consistency in results may be related to differences among studies in the control over confounding factors,^{14,15} with some studies not controlling for factors such as birth weight (BW) and gestational age (GA),^{16,17} neurologic insults,¹⁶⁻¹⁸ and obstetric complications.¹⁶ Maternal cigarette smoking was also often not considered in the research design or data analysis of studies assessing the risks of fetal cocaine exposure.^{19,20} Impairments on the NBAS may be more likely among infants whose mothers smoked cigarettes during pregnancy.²¹⁻²⁴ The results of more recent and better-controlled studies have yielded inconsistent results with some studies finding adverse effects of fetal cocaine exposure on some NBAS scores during the first month of life²⁵⁻³³ and others reporting no adverse effects.³⁴⁻³⁶ The most common findings on the NBAS were cocaine-associated disturbances on measures assessing state regulation.^{16-18,25-30,32,33}

The NBAS may not be sufficiently sensitive to detect subtle cognitive disturbances which may be associated with abnormal development of the CNS among cocaine-exposed neonates. The NBAS in-

cludes measures of orientation and habituation to an initial stimulus, but Zelazo and colleagues³⁷ demonstrated that it is response to change, ie, recovery of responding and habituation to novelty after habituation to an initial stimulus, that has the greatest sensitivity and validity for identifying neonates at risk for subsequent developmental delays. The NBAS does not measure response to change. A large series of carefully controlled studies using the auditory information processing procedure developed by Zelazo and colleagues³⁸⁻⁴³ has demonstrated that newborn infants orient and habituate to an auditory stimulus and recover responding to novelty with little variability across studies. Habituation and recovery to novelty in infancy correlate with measures of intellectual competence in childhood, suggesting that these measures assess infant central processing^{44,45} (see "Reference 45" for direct experimental tests of competing interpretations). Delayed mental ability results in decreased speed of processing on measures of infant information processing.^{37,46} If cocaine interferes with normal CNS development, decreased speed of processing may be evident on measures of habituation and recovery during the neonatal period.

Existing studies assessing the effects of fetal cocaine-exposure on information processing ability in infancy have used visual stimuli and yielded inconclusive results.⁴⁷⁻⁵⁰ Mayes and colleagues⁴⁷ reported that although cocaine-exposed infants were more likely to fail to begin a visual habituation and novelty responsiveness task, those that completed the task did not differ from controls on habituation or response to novelty. Struthers and Hansen⁴⁸ used the Fagan Test of Infant Intelligence (FTII) to study the effects of prenatal cocaine exposure on infant visual information processing. Overall, FTII scores were significantly lower among the drug-exposed infants relative to controls, with 17 of the 36 drug-exposed infants scoring in the at-risk range compared with only 3 of the 26 controls. However, only 47% of the drug-exposed sample were exposed to cocaine and not amphetamines, a number of the mothers had also used significant quantities of alcohol, marijuana, and opiates, and cigarette use was not documented. In one well-controlled, longitudinal study, Jacobson and colleagues⁴⁹ found that heavy cocaine use early in pregnancy was related to poorer recognition memory and visual information processing as measured by the FTII. Alessandri and colleagues,⁵⁰ however, failed to find deficits in novelty responsiveness or information processing in their study of 8-month-old cocaine-exposed infants. At present, there are no studies of which we are aware that have assessed information processing during the early neonatal period and none in which auditory stimuli were used.

Several studies have reported language impairments⁵¹⁻⁵⁸ and attentional problems⁵⁹ on follow-up assessments of children exposed to cocaine in-utero, supporting the notion that cocaine may adversely affect the development of higher cortical processes. A recent meta-analysis revealed that cocaine has a significant detrimental effect on the receptive and expressive language abilities of children exposed

prenatally, as well as a small but significant adverse effect on IQ.⁶⁰ However, studies on the effects of prenatal cocaine exposure on subsequent language development of the child are often subject to methodologic problems such as lack of control groups, retrospective designs, small sample sizes, maternal polydrug use, nonblind examiners, and lack of control over confounding factors. For this reason, the results of such studies should be interpreted with caution. Because maternal cocaine use is generally associated with a host of other biological and environmental risk factors for disturbances in children's cognitive development, such as multiple substance use, lack of prenatal care, poverty, and child neglect, it is difficult to isolate prenatal cocaine exposure as the singular cause of impaired language development. Nevertheless, there is a growing body of data⁵¹⁻⁵⁸ to suggest that prenatal cocaine-exposure may be associated with disturbances in language development.

If fetal cocaine exposure is associated with impaired language development, it may be more appropriate to assess auditory rather than visual information processing in early infancy to evaluate possible intrauterine influences. The relative contributions of intrauterine cocaine exposure and postnatal environment to later cognitive development are virtually impossible to disentangle retrospectively. However, if language impairments are a result of disturbances in fetal brain development among children exposed to cocaine in utero, then such disturbances may be detectable at birth using tests of auditory information processing.

In the present study, the information processing procedure developed by Zelazo and colleagues^{37-43,45} was used to assess newborn central processing of auditory stimuli. It was hypothesized that cocaine exposure in utero can alter neurologic development and this may be detected at birth by abnormal auditory information processing. Specifically, it was hypothesized that cocaine-exposed neonates would be less likely than nonexposed neonates to respond to stimulus change after habituation to a previously presented stimulus.

METHODS

The procedures followed in this study were in accordance with the ethical standards of the Canadian and American Psychological Associations, and were approved by the institutional review boards of the Sir Mortimer B. Davis Jewish General Hospital, Montreal Children's Hospital, and McGill University. Mothers on the postpartum ward were approached about participating in the study and the nature of the study was explained in detail, including the fact that if they admitted to using cocaine or if cocaine was detected by biological assay that we would be required to report this to Social Services. All cocaine users who agreed to participate were already known to Social Services and were being followed by a social worker at the time of delivery. Signed informed consent forms were obtained from each mother before testing her infant. Each mother was aware that she was free to withdraw from the study at any time and that this would in no way affect her care at the hospital or her treatment by Social Services, and that, with the exception that drug use must be reported, all data obtained in the course of the study would be kept confidential.

Participants

Twenty-five cocaine-exposed and 25 nonexposed control neonates, matched in a case-controlled design, were tested on an

auditory information processing procedure. Neonates with brain hemorrhages or any other clear neurologic insults (such as hydrocephalus, spina bifida, seizures) were excluded and all infants had 5-minute Apgar scores of 7 or greater. Preterm infants were not excluded but cocaine-exposed and control infants were matched on GA and BW. Prenatal exposure to cocaine was determined by maternal self-report obtained through a questionnaire about drug use during pregnancy completed by the mother after the delivery of her infant ($n = 21$ positive self-reports), meconium analysis ($n = 8$ positive samples), and/or 1 cocaine-positive urine sample from the infant ($n = 16$ positive samples). Because urine analysis can detect only recent cocaine use (within a few days) and self-reports of no drug use may be unreliable, it was important that all control infants had negative meconium analysis results to increase the likelihood that cocaine-exposed infants were not inadvertently included in the control group. Because positive urine tests for cocaine and/or maternal self-reports of cocaine use were deemed to be reliable indicators of prenatal cocaine use, where 1 of these indicated cocaine use, a lack of meconium analysis results was not considered problematic.

Cocaine-exposed neonates were individually matched with control neonates on at least 3 of the following 5 variables: a) GA within 2 weeks; b) BW within 450 g; c) number of cigarettes, within 5, smoked per day; d) socioeconomic status as reflected by household income (SES) within \$10 000 per year; and e) mother's pregnancy weight gain (WG) within 5 kg. It was not possible to match all infant pairs on all 5 variables. However, all cocaine-exposed infants whose mothers smoked cigarettes were paired with noncocaine-exposed infants whose mothers smoked. Furthermore, all pairs matched on at least 3 criteria, 18 pairs matched on at least 4 criteria, 10 pairs matched on all 5 criteria, and there were no significant differences between the cocaine-exposed and control groups on any of the matching variables. A power analysis indicated that with 25 infants in each group, the power to detect a large effect size was .80.⁶¹ There were 15 females and 10 males in the cocaine-exposed group, and 16 females and 9 males in the nonexposed control group; in 16 of the 25 matched pairs, the infants were of the same gender. Although preterm infants were not excluded from the study, care was taken to ensure that there were equal numbers of preterm infants in each group, and that preterm infants in each group were matched on GA and BW. Previous research using the auditory information processing procedure showed that infants with GA <30 weeks demonstrate normal orientation and habituation³⁷; however, in the present study post hoc analyses were conducted to test empirically whether the inclusion of preterm infants accounted for any observed differences between the cocaine-exposed and control infants. Of the 25 infants in each group, 5 cocaine-exposed and 5 control neonates had GAs between 28 and 36 weeks. Infant conceptional age and weight at the time of testing, Apgar score at 5 minutes after delivery, maternal age, and extent of prenatal care (CARE) were also analyzed for between-group differences, and gestational alcohol and drug use were documented. Group means and standard deviations for the matching variables and other demographic variables are shown in Table 1.

Multivariate analysis of variance indicated that the cocaine-exposed and control neonates were similar on all matching and demographic variables except CARE, $F(1,48) = 22.79$, $P < .001$; 24 control mothers and 14 cocaine-using mothers received prenatal care. With the exception of CARE, none of the univariate F -tests was significant. Because lack of prenatal care is a risk factor for adverse pregnancy outcome, cocaine-exposed neonates whose mothers had received prenatal care were compared post hoc on the information processing measures with those who had not.

The majority of neonates were tested on the information processing procedure between 18 and 72 hours of age (cocaine-exposed: $n = 13$; controls: $n = 21$). Preterm neonates were tested as soon as possible once medically stable. Of the 12 cocaine-exposed infants who were not tested within 72 hours of birth, 5 were tested within 8 days, and the remaining 7 were tested between 2 and 6 weeks of age. Of the 4 control infants who were not tested within 72 hours of birth, 2 were tested between 1 and 3 weeks of age, and the remaining 2 were tested at 4 and 6 weeks of age. The most common reason for delay in the testing of the cocaine-exposed neonates was difficulty locating the mothers to obtain informed consent because they left the hospital shortly after giving birth. Previous research indicates that infants demonstrate orientation,

TABLE 1. Group Means and Standard Deviations for Cocaine-Exposed and Control Neonates on the Five Matching and Five Control Demographic Variables

Variable	Cocaine (<i>n</i> = 25)	Controls (<i>n</i> = 25)
Subject matching variables		
Gestational age (wk)	37.3 (2.8)*	37.5 (2.7)
Birth weight (g)	2679 (636)	2827 (597)
Number of cigarettes smoked/day†	13.7 (10.1)	10.6 (8.8)
SES (\$1000 per year)	16.2 (14.2)	19.9 (17.5)
Maternal weight gain (kg)	12.1 (4.2)	12.7 (4.0)
Control variables		
Corrected gestational age at testing (wk)	39.0 (2.5)	38.1 (2.0)
Weight at testing (g)	2887 (577)	2832 (489)
Apgar at 5 min	8.8 (0.6)	9.1 (0.5)
Mother's age (y)	27.2 (4.3)	27.0 (5.9)
Number who received prenatal care	14/25	24/25‡

Abbreviation: SES, socioeconomic status as reflected by household income.

* Standard deviations are listed in parentheses beside each group mean.

† Includes all participants with nonsmokers receiving a score of 0. ‡ $P < .001$.

habituation, and recovery for several weeks after birth on the auditory information processing procedure.³⁷ To ensure that the delay in testing of some cocaine-exposed infants in the current study was not associated with reduced head-turning, the principal dependent variable, cocaine-exposed neonates tested within 72 hours of birth were compared with those tested at a later date on the percentage of head-turns made. There was no difference between the groups, $t(23) = .37, P = .72$.

Maternal Drug Use

Meconium samples, collected from the neonates' diapers, were available for all 25 control and 15 cocaine-exposed neonates. Among the 15 cocaine-exposed neonates for whom meconium samples were available, 8 tested positive for cocaine. The 7 cocaine-negative meconium samples were consistent with maternal self-reported cessation of cocaine use by the second trimester, that is, before meconium analysis can reliably detect cocaine use. Where meconium samples were not available, fetal cocaine exposure was determined based on neonatal urine analysis and maternal self-report.

Meconium was analyzed for cocaine, benzoylecgonine (BE), cocaethylene, opiates, cannabinoids, and cotinine using the method described by Clark and colleagues⁶² which has >99.9% sensitivity and specificity for the detection of cocaine and BE. Urine analyses were performed using a commercial radioimmunoassay.

Maternal drug use was assessed also via a self-report questionnaire completed by the mother at the time she agreed to participate in the study. Table 2 summarizes the estimated extent of maternal cocaine use, based on self-report, with quantities averaged across gestation, classified along a 4-point continuum. Quantification of cocaine and BE metabolites was provided by meconium analysis; however, this information was not used in estimating the extent of maternal cocaine use because it is known

TABLE 2. Classification of Cocaine Users by Quantity and Frequency of Use*

Cocaine Use	Light	Moderate	Heavy	Very Heavy
<i>n</i> of 25	8	8	6	3
Percentage of users	32	32	24	12

* Cocaine use was divided into 4 categories as follows: light, cocaine use limited to the first trimester, <.5 g, less than once per week; moderate, use throughout gestation, 0.5 g or less between 1 and 3 times per week; heavy, use throughout gestation, .25–1 g daily; very heavy, use throughout gestation, more than 1 g daily. For 3 mothers who failed to complete the questionnaire, the extent of cocaine use was estimated from social work records.

that there is variability in the placental transfer of cocaine to the fetus,⁶³ and also because the single meconium samples available for some infants might not provide accurate quantification of overall cocaine exposure. The primary method of cocaine administration was via the nasal route, although a small percentage of the cocaine-using sample also reported smoking crack and/or administering cocaine intravenously. Self-reported cocaine consumption ranged from .25 g once per month in the first trimester to 3 g per day throughout gestation. As is typical of studies involving intranasal cocaine use, no information about the purity of the cocaine used was available.

Maternal use of alcohol and other substances during pregnancy is summarized in Table 3. Equal numbers of mothers in each group smoked cigarettes. None of the mothers in either group reported heavy drinking or extensive use of marijuana/hashish, with the exception of 1 cocaine-user who reported drinking 8 beers per occasion, twice per month. Apart from this participant, the maximum reported regular use of alcohol was 2 drinks per occasion, once per week throughout pregnancy, reported by 1 control mother and 3 cocaine-using mothers. Additionally, only 2 of the cocaine-using mothers and 2 of the control mothers reported using marijuana/hashish beyond the first trimester of pregnancy, and in all cases, the amounts were small (eg, 1 joint every 2 weeks). Based on self-report, 3 of the cocaine-using mothers also used heroin, with use limited primarily to the first trimester. One participant took 1 point on 2 occasions in the first trimester and again in the third trimester; another participant took one quarter of 1 point daily during the first trimester; and the third participant reported heroin use in the first trimester only, but did not specify the quantity or frequency. Heroin, marijuana, and cocaine were the only illicit substances reportedly used by the women in this study. None of the meconium samples tested positive for opiates. Three cocaine-exposed and 1 control neonate tested positive for cannabinoids. Only 1 meconium sample tested positive for cocaethylene, suggesting that the majority of cocaine-using women in this sample did not abuse alcohol in addition to cocaine.

χ^2 analyses indicated that the number of mothers in each group who drank alcohol or used heroin did not differ. However, significantly more cocaine-using mothers used cannabis than noncocaine-using mothers, $\chi^2(1) = 6.57, P = .01$. To determine if prenatal exposure to cannabis affected the performance of the cocaine-exposed neonates on the information processing procedure, cocaine-exposed neonates whose mothers had used cannabis were compared post hoc on the information processing measures with those who had not.

Information Processing Procedure

Two spoken words were played through stereo speakers, 30 cm to either side of the neonate's ears, at a sound pressure level of 72 decibels. "Tinder" and "beagle," demonstrated previously to be discriminable by neonates,^{37,38} served as the stimuli. Neonatal responses were coded on a hand-held box and delivered on-line to the computer which kept track of trial duration, and occurrence and duration of each of the 4 possible responses: head-turn to the right, head-turn to the left, fretting, and eyes closed.

Neonates were tested 30 to 60 minutes after feeding, once a fully awake, alert, quiet state was achieved. Throughout the pro-

TABLE 3. Number of Cocaine-Using and Control Mothers Who Used Other Substances

Substance Used*	Cocaine (<i>n</i> = 23)†	Controls (<i>n</i> = 23)‡
Cigarette smoking	20	20
Any alcohol use	15	12
Alcohol use throughout pregnancy	7	3
Marijuana/hashish (any use)§	9	2
Heroin (any use)§	3	0

* Based on self-report, although use of cannabinoids and heroin after 20 weeks of gestation could be detected by meconium analysis.

† Missing data for 2 of the 25 participants.

‡ Missing data for 2 of the 25 participants.

§ Cocaine, marijuana, hashish, and heroin were the only illicit substances reportedly used; heroin was used regularly by only 1 participant.

cedure, the neonate was held by 1 experimenter (the holder) at a 45-degree angle between vertical and supine, as recommended by Muir and Field.⁶⁴ A second experimenter (the coder) recorded the neonate's responses on the button box. A head-turn was coded when the infant rotated the sagittal midline of the head 45 degrees to either side. A third experimenter (the presenter) controlled the computer and apparatus delivering the stimuli. To eliminate experimenter bias, the holder and coder wore stereo headphones which delivered both auditory stimuli simultaneously to both ears, giving the impression of central location of the sound, thereby eliminating the possibility that the holder or coder could hear the particular stimulus or the direction of the stimulus presented to the infant. Thus, only the stimulus presenter was aware of the direction of the sound presented to the infant, the particular stimuli delivered, and changes from one phase of the procedure to the next. Although efforts were made to blind the experimenters to the infants' drug exposure status, for 11 (22%) of the 50 participants, the holder or coder knew that the infant was cocaine-exposed. Thus, the experimenters were blind to drug-exposure status for 78% of the infants tested. However, because the holder and coder were blind to the stimulus being delivered to the infant and were, therefore, not aware of changes from one phase of the procedure to the next, nor the direction of the stimulus, it was virtually impossible for these experimenters to influence an infant's performance.

Each neonate participated in 3 phases of the information processing procedure in a partial infant-controlled design³⁷: a) familiarization phase: the familiarization word was presented until criteria for orientation and habituation were achieved, or for 16 trials if the infant failed to orient; b) novelty phase: a novel word was played until the infant oriented and habituated, or for 12 trials if the infant failed to orient; and c) dishabituation phase: the initial familiarization word was presented again until the infant oriented, or for 9 trials if the infant failed to orient.

The criterion for orientation in each phase was defined as 3 head-turns toward the sound within 4 consecutive trials. The criterion for habituation was any combination of head-turns away and/or lack of a head-turn within 3 consecutive trials. In each phase, 1 stimulus, ~1 s in duration, was presented to the neonate repeatedly at a rate of 1 word every 2 s, in trials of 30 s maximum duration. If a head-turn was sustained for 3 s or if no turn occurred before 30 s had elapsed, the trial ended. Intertrial intervals were ~5 to 10 s in length. When the neonate reached the criteria for orientation and habituation or the maximum number of allowable trials for each phase, the word was changed by the experimenter presenting the stimuli and the next phase began. The holder and coder were not aware of when infants reached the criteria for orientation and habituation or changes from one phase of the procedure to the next.

Data Reduction and Study Design

The principal dependent variable was the percentage of trials which ended with head-turning toward the sound in each trial block. To determine if the direction of head-turns approached chance levels, a difference score was calculated for each trial block by subtracting the number of turns away from the number of turns toward the sound. The familiarization phase was divided into 2 trial blocks for 1 set of analyses and 4 quartiles for other analyses. This was repeated for the novelty phase. For the dishabituation phase, the first 3 to 6 trials served as the trial block. Multivariate analyses of variance were conducted with group (cocaine-exposed/control) as the independent variable and trial blocks as a repeated measure. *t* tests were used to compare difference scores with a mean of zero. For both groups, the percentage of infants who reached criteria for orientation and habituation were compared using χ^2 analyses. The number of trials required to reach criteria for orientation and habituation were examined using analyses of variance.

RESULTS

Control Variables

Analysis of variance of the overall percentage of trials ending with a head-turn indicated that the cocaine-exposed (mean = 74.2% of trials) and control neonates (mean = 77.9% of trials) produced equal

numbers of head-turns during the procedure. Moreover, cocaine-exposed and control neonates spent equivalent, high percentages of time in an alert, non-fretting state, although this tended to decrease linearly across phases, $F(2,47) = 2.09$, $P = .05$ (means = 87.1%, 84.0%, and 81.6% for the familiarization, novelty, and dishabituation phases, respectively).

Information Processing

The performances of the cocaine-exposed and control neonates across the 3 phases of the information processing procedure are shown in Fig 1 (panels a, b, and c).

Familiarization Phase

A repeated measures multivariate analysis of variance indicated that, collapsed across group, the percentage of head-turns toward the sound decreased across the quartiles of the familiarization phase confirming that neonates habituated to the stimulus, $F(3,46) = 15.52$, $P < .0001$ (Fig 1, panel a). The percentage of head-turns toward the sound was similar for both groups during the first 3 quartiles, although cocaine-exposed neonates tended to turn toward the sound more often than controls during the fourth quartile $F(1,48) = 3.19$, $P = .08$. Eighty percent of the cocaine-exposed neonates and 88% of controls reached the criterion for orientation (not significant) and both cocaine-exposed, $t(24) = 5.17$, $P < .001$, and control neonates, $t(24) = 3.62$, $P < .01$, turned preferentially toward the stimulus during the first quartile. However, only 44% of cocaine-exposed neonates habituated compared with 76% of controls, $\chi^2(1) = 5.33$, $P < .05$. Moreover, during the last quartile of the familiarization phase, the control neonates turned systematically away from the stimulus $t(24) = -3.73$, $P < .01$, whereas the direction of head-turning was random for cocaine-exposed neonates.

Novelty Phase

A comparison of the percentage of head-turns toward the sound during the last trial block of the familiarization phase with the first trial block of the novelty phase indicated that control neonates recovered responding whereas cocaine-exposed neonates did not, $F(1,48) = 21.07$, $P < .001$ (Fig 1, panel b). Turns toward the stimulus increased from the last block of the familiarization phase (mean = 34.4%) to the first block of the novelty phase (mean = 67.9%) for control neonates, but remained relatively stable from the familiarization block (mean = 40.4%) to the novelty block (mean = 36.8%) for cocaine-exposed neonates. Excluding neonates who failed to habituate to the familiarization stimulus did not change the results; cocaine-exposed neonates continued to show a lack of recovery to novelty relative to controls, $F(1,28) = 9.07$, $P < .01$. Moreover, they displayed lower levels of head-turning toward the novel stimulus than they had to the familiarization stimulus during orientation, $t(24) = 4.16$, $P < .0001$, unlike control neonates who responded to novelty at the same level as initial orientation.

Ninety-two percent of the control infants oriented

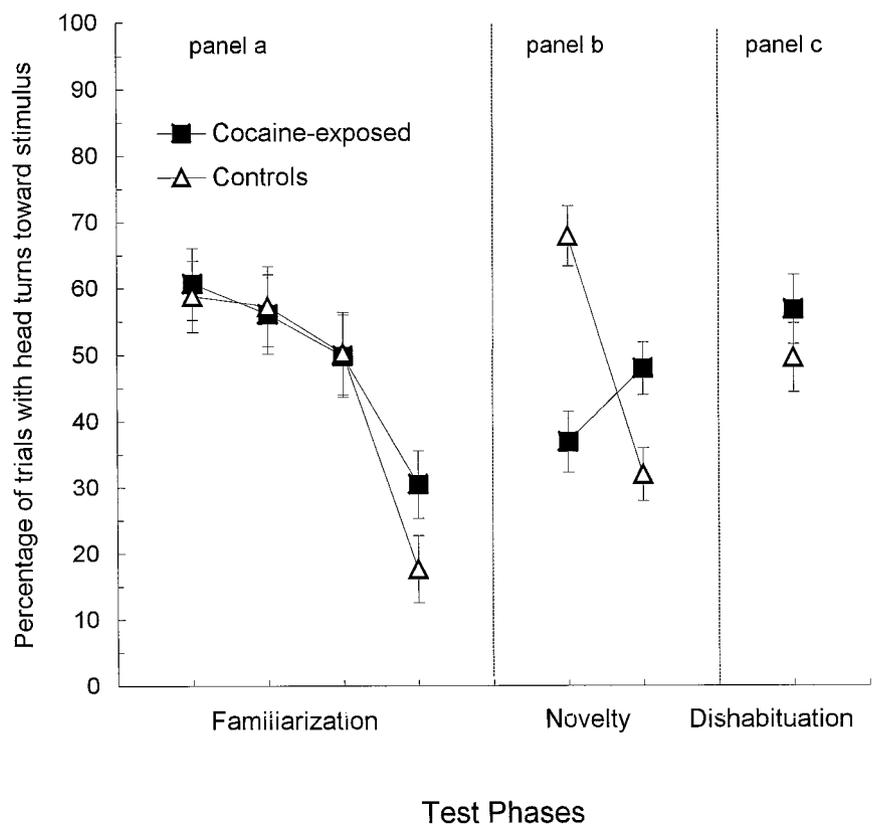


Fig 1. Mean percentage of head-turning toward the sound for cocaine-exposed and control neonates during: familiarization phase quartile blocks (panel a); novelty phase trial blocks (panel b); and the dishabituation phase trial block (panel c).

to the novel stimulus compared with 48% of the cocaine-exposed newborns, $\chi^2(1) = 11.52, P < .01$, averaging 5.2 and 8.0 trials, respectively, to reach criterion $F(1,33) = 6.72, P < .05$. Similarly, 72% of the control neonates habituated to the novel stimulus compared with only 12% of the cocaine-exposed newborns $\chi^2(1) = 18.47, P < .001$, averaging 10.4 and 12.8 trials, respectively. Analyses of difference scores indicated that control neonates turned systematically toward the novel stimulus in the first quartile, $t(24) = 6.26, P < .001$, and away from the stimulus in the last quartile, $t(24) = -4.06, P < .001$. In contrast, the cocaine-exposed neonates turned randomly in the first quartile, and turned systematically toward the novel stimulus, $t(24) = 3.73, P < .01$, in the last quartile, when habituation and turning away are expected.

Dishabituation Phase

Inspection of Fig 1 (panels b and c) revealed that head-turning toward the sound for cocaine-exposed neonates was higher than for control neonates during both the last trial block of the novelty phase and the dishabituation trial block (although not statistically), reflecting an apparent trajectory of increasing responsiveness and rendering a between-group comparison inappropriate. Therefore, within group tests were calculated for comparison of the percentage of head-turns toward the stimulus in the second block of the novelty phase with the dishabituation trial block. Only control neonates recovered responding to the dishabituation stimulus, $t(24) = 2.33, P < .05$; cocaine-exposed neonates did not, $t(24) = 1.63, P > .10$.

Pearson product moment correlations were conducted to determine if the extent of cocaine use, as shown in Table 2, was related to performance on the information processing procedure. Results showed that extent of cocaine use, classified along a 4-point continuum from light to very heavy use, was not related to any of the information processing measures. It is likely, however, that the lack of relation between the extent of cocaine exposure and newborn information processing ability may be because of the breakdown of the relatively small sample size ($n = 25$) according to cocaine-usage scores (as low as 3 per cell for the very heavy users).

Post Hoc Analyses

Influence of Inclusion of Preterm Infants

Preterm infants were included in the study sample because preterm delivery is not associated with impaired orientation and habituation,³⁷ preterm delivery has been frequently associated with cocaine use in the literature,^{65,66} and because exclusion of preterm infants would decrease statistical power. However, it was of interest to determine if the findings were maintained when preterm infants were excluded. To answer this question, the data were reanalyzed with the 10 preterm infants excluded (5 cocaine-exposed and 5 control infants). The exclusion of the preterm infants did not alter the results; analyses of all measures which had discriminated between the cocaine-exposed and control infants remained significant.

Influence of Prenatal Care and Cannabis Use

A comparison of the 14 neonates of the cocaine-using mothers who received prenatal care with the

11 neonates of mothers who did not, revealed that prenatal care had no impact on neonatal auditory information processing ability. There were no differences between neonates who received prenatal care and those who did not on any of the information processing measures that discriminated between the cocaine-exposed and control neonates. Similarly, when the cocaine-exposed infants whose mothers had used cannabis were compared with those who had not, there were no group differences on any of the information processing measures.

DISCUSSION

The results of this study reveal clear and consistent differences between cocaine-exposed and control neonates on auditory information processing measures. Fewer fetal cocaine-exposed neonates habituated to the familiarization stimulus and they turned randomly, rather than away from the sound, during the habituation trial block. They displayed lower levels of head-turning toward the novel word, did not recover to initial levels of orientation, did not habituate to novelty, showed random turning toward and away from the novel stimulus, and did not recover to the reappearance of the familiarization stimulus.

These results clearly indicate that auditory information processing was impaired for cocaine-exposed neonates. Cocaine-exposed and control neonates in this study were matched on numerous potential confounding factors including GA, BW, SES, WG, and number of cigarettes mothers smoked during pregnancy. The cocaine-exposed and control groups were similar in terms of the mother's age, the age and weight of the infant at the time of testing, and infant Apgar scores at 5 minutes. Moreover, although fewer cocaine-using mothers received prenatal care, a comparison of neonates whose mothers who received prenatal care with those who did not, revealed no differences on any measures of information processing. As well, the information processing performance of infants exposed to cannabis in addition to cocaine did not differ from that of the cocaine-exposed infants who were not exposed to cannabis. The extent of cocaine use by the mother was not related to information processing performance; infants whose mothers reported that they were light users of cocaine did not differ on the information processing measures from those who reported they were heavy users (although it is possible that this lack of relation was because of the relatively small sample size). Cocaine-exposed and control neonates made comparable numbers of head-turns during the procedure and exhibited high levels of positive state. When preterm infants were excluded from the data analyses, the results did not change; cocaine-exposed infants exhibited the same pattern of impaired information processing compared with controls. Together, these results imply that the deficits in information processing ability among the cocaine-exposed newborns are directly related to intrauterine cocaine exposure, not to preterm delivery, neurologic or physical limitations, or to extrauterine experiences.

The auditory information processing procedure

used in this study has been shown to elicit a reliable pattern of responding among neonates in numerous well-controlled studies.^{37-43,45} Using this procedure, newborn infants consistently demonstrate orientation and habituation to an auditory familiarization stimulus and recovery to a novel auditory stimulus. Moreover, recovery to novelty was shown to discriminate between neonates at high-, moderate-, and low-risk for subsequent developmental delay³⁷ indicating that the procedure has good discriminant validity and is, therefore, appropriate for assessing the effects of intrauterine cocaine exposure.

In the present study, the within-subjects controls used in this procedure yielded cumulative effects across experimental phases so that neonates who did not habituate to the familiarization stimulus did not recover or habituate to the novel stimulus or dishabituate to the reappearance of the familiarization stimulus. These results are similar to those found with high-risk neonates³⁷ using the same paradigm. We believe that, as with high-risk outcomes, these data reveal slower speed of processing for cocaine-exposed neonates, an interpretation that has received support from studies with older, noncocaine exposed children.^{46,67} Slower processing speed is a characteristic of the organism that continues over testing explaining why the effects are cumulative. Results from the present study reveal disrupted information processing at birth and imply that fetal cocaine exposure interferes with structures in the brain that are involved in auditory processing.

Cocaine exerts its psychotropic effects primarily through its actions on monoaminergic neurotransmitters. Monoaminergic neurotransmitter systems develop much earlier in the fetus than most other neuronal systems⁶⁸ and seem to play a key role in controlling the development of other brain areas.^{8,69} Developing neuronal systems are particularly vulnerable to the teratogenic influences of drugs which interfere with the metabolism of monoamines.⁷⁰

Impaired performance on the information processing measures may be related to the increased brainstem transmission time for auditory stimuli that has been associated with fetal cocaine exposure in some studies.^{71,72} Delays in the transmission of auditory stimuli to the cerebral cortex could result in delayed encoding and storage of auditory stimuli. However, Salamy et al⁷² found that by ages 3 to 6 months cocaine-exposed infants were indistinguishable from controls on measures of auditory brainstem transmission time, suggesting that the adverse effects of cocaine on the processing of auditory information may be transient. Nevertheless, the fact that the cocaine-exposed neonates in our study showed the same degree of orientation to the familiarization stimulus as the controls suggests that the group differences on measures of habituation and recovery to novelty are not because of delays in brainstem auditory transmission time.

Cocaine-exposed infants have been described by some researchers as being over-reactive to a variety of stimuli.³² Thus, it might be suggested that the failure of the cocaine-exposed infants to habituate to the familiarization stimulus to the same degree as the

control infants is because of this hyperresponsivity. However, the fact that the level of head-turns toward the stimuli varied considerably among cocaine-exposed neonates during the course of the procedure but increased and decreased at inappropriate times, along with the fact that the overall number of head-turns did not discriminate between groups, reduces the likelihood that increased reactivity among cocaine-exposed infants accounts for the observed group differences in information processing.

The auditory information processing deficits observed among fetal cocaine-exposed infants during the neonatal period in the present study may be a precursor to the impaired attention and language abilities observed in some studies of prenatally-exposed preschool and primary school-aged children.^{12,51-59} If the deficits observed in the central processing of auditory information among cocaine-exposed newborns are a manifestation of cerebral dysfunction, then the fact that these deficits were observed before the postnatal environment had a chance to impact on infant development implies that fetal cocaine exposure may play a causal role in the development of the observed childhood attention and language impairments. However, cocaine use during pregnancy is associated with a constellation of other risk factors such as cigarette smoking, use of other illicit drugs, and poverty, among other things. The cocaine-exposed infants in the present study were matched with control infants on many of these potentially confounding variables (GA, BW, number of cigarettes per day, SES, and WG), but perfect matching was impossible to achieve. Although the groups did not differ statistically on any of the matching variables, the cocaine-exposed group tended to compare unfavorably with the nonexposed group overall; that is, on average, the cocaine-using mothers smoked 3 cigarettes per day more than the controls, had incomes \$3700 less per year, and their infants weighed 150 g less at birth. Also, more of the cocaine-using mothers drank alcohol and used other drugs. These differences were relatively small, but may have had a cumulative effect that adversely influenced the performance of the cocaine-exposed infants or compounded the adverse effects of the fetal cocaine-exposure. There is evidence from studies using the NBAS that maternal prenatal cigarette smoking may be associated with impaired auditory information processing²¹⁻²⁴; thus, it is possible that the slightly higher cigarette consumption of the cocaine-using mothers adversely affected the performance of their infants on the current auditory information processing procedure relative to controls. In addition, no information was available about the purity of the cocaine used by the mothers in this study; it is, therefore, possible that the observed differences between the cocaine-exposed and nonexposed infants were partially because of other substances in the cocaine which could potentially alter CNS function (such as amphetamines, PCP, and other psychoactive compounds). Cocaine use is typically associated with a constellation of other risk factors, and the data from this study provide strong evidence that prenatal cocaine exposure, either alone

or in combination with these other risk factors, has detrimental effects on the subsequent auditory information processing ability of newborn infants.

Implications

Clearly, fetal exposure to cocaine may have negative implications for the cognitive abilities of infants, particularly auditory information processing and receptive and expressive language development. However, the findings of the present study are limited to the newborn period, and it is possible that the auditory information processing deficits are transient. The infant brain demonstrates remarkable plasticity and once free from exposure to cocaine, recovery of function may occur. It is also possible that the auditory processing deficits are a more permanent reflection of CNS impairment that occurred in utero. Well-controlled, long-term follow-up studies are warranted to determine if performance on the auditory information processing procedure is predictive of later cognitive competence, particularly language abilities.

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