Measuring the Effects of Prenatal Cocaine Exposure

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The effects of prenatal exposure to cocaine are of great interest to the research, clinical, and educational communities. As Vorhees and Neuspiel report in this volume, there have been few striking, consistent findings reported thus far in either animal or human studies. It is our belief that the failure to find robust results, particularly in human follow-up studies, is related to three problems inherent in this type of research: identification and quantification of drug use, confounding variables, and insensitive and limited outcome measures.

IDENTIFICATION AND QUANTIFICATION OF DRUG USE

Identifying the specifics of maternal drug use presents a methodological problem for studies of prenatal exposure. It is evident that amount, timing over the course of gestation, pattern of use, and use of other substances that might potentiate the effects of cocaine, are impossible to ascertain reliably for every drug user given the current state of technology. (See Ostrea, chap. 10, this volume, for a more detailed presentation of these issues.) Moreover, animal models cannot adequately address all of the issues of timing, route of administration, and drug use pattern. These problems are discussed more fully in other chapters of this volume.
CONFOUNDING VARIABLES

The effects of the multitude of variables other than substance use that tend to covary with a drug-using lifestyle, and that are related to developmental outcome presents another difficulty. The offspring of drug users are at high risk of developmental problems from such prenatal factors as poor maternal nutrition, high maternal stress levels, and poor maternal health, to list but a few. There are similarly numerous postnatal variables, known to impact a child’s development, which may not be optimal for the children of drug users. These include obvious extreme conditions, such as neglect or exposure to violence as victim or witness. There may be inconsistent and numerous caregivers, and the child may have no one with whom to engage in sensitive, responsive, and appropriately stimulating interactions. Most of the children we study live in materially impoverished conditions, and are thus at risk due to suboptimal environments even without being exposed to toxins. Studies have not always considered confounding variables or have controlled for very few. The Jacobsons, Neuspiel, and other contributors to this volume, discuss this issue further.

MEASURING OUTCOMES

The third problem is the relative scarcity of studies that have considered sufficiently sensitive and wide-ranging outcome measures. The majority of human studies of prenatal cocaine exposure to date have examined only two measures—the Brazelton Neonatal Behavioral Assessment Scale, and the Bayley Scales of Infant Development. Studies examining performance on the Brazelton have failed to replicate a pattern of significant findings (e.g., Chasnoff, Burns, Schnoll, & Burns, 1985; Coles, Platzman, Smith, James, & Falek, 1992; Eisen et al., 1991; Mayes, Granger, Frank, Schottenfeld, & Bornstein, 1993; Neuspiel & Hamel, 1991). Moreover, the stability and long-term significance of a single Brazelton score obtained soon after birth have been questioned (Brazelton, 1987). Similarly, Bayley scores in the average range have poor predictive validity (Bornstein & Sigman, 1986; Lewis & McGurk, 1972; McCall, Hogarty, & Hurlburt, 1972). In addition, global or aggregate measures of functioning, such as those derived from the Bayley, often mask more specific deficits, for example language or fine motor problems. The issue of measuring outcome has not been addressed extensively and is the focus of this chapter.

MEASURE OR MEASURES: THE VALUE OF MULTIPLE, SENSITIVE, AND PREDICTIVE OUTCOMES

Single global measures of ability, such as IQ, generally assess skill across a variety of functional domains. These usually include language, perception, fine motor, visual-motor integration, memory, and abstract reasoning. Whereas a mas-
sive, early insult to the brain may result in general deficits of cognitive and motor functioning, most insults affect much more circumscribed regions or systems of the brain. In addition, central nervous system (CNS) development is relatively lengthy and the timing of a perturbation is an important determinant of impact. Therefore, the majority of insults would be expected to have relatively specific developmental sequelae. An IQ score is analogous to pureeing potatoes, zucchini, onions, and turnips. Various felicitous combinations will produce a decent tasting soup, but will make individual flavors indistinguishable. If perturbation X causes a deficit in Skill A but not Skill B, and the subject is unusually good at Skill B, it would appear that X had no effect at all on the total A + B ability. Thus, limiting our outcome measure to IQ may mask specific effects of particular perturbations.

Another problem of the IQ score is that the tests rely on motor ability in the first 18 months of life, but at older ages, depend on language competence for adequate performance. Thus, an IQ score for an infant informs us mostly about fine motor ability, and for an older child, about language competence. This is one of the reasons that infant IQ scores are not predictive of later ones; that is, early motor ability may be unrelated to language skill (Lewis, Jaskir, & Enright, 1986; Lewis & McGurk, 1972; McCall, Eichorn, & Hogarty, 1977).

It seems clear that we must measure many different functions to begin to study the specific impact of a particular insult such as prenatal cocaine exposure. The region or system of the brain affected by a perturbation, whether the impact is discrete or global, and its timing during CNS development are all likely to affect whether and what specific functional deficits may result. In addition, the young brain is inherently plastic and may have the capacity to compensate for damage, especially if the external environment provides appropriate stimulation (Lee & Barratt, 1993).

In a study of the effects of intraventricular hemorrhage (IVH) on the development of preterm infants, we have taken an approach that underscores the value of using multiple outcomes and accounting for the effect of several confounding variables. As IVH is, like prenatal cocaine exposure, an early CNS insult associated with both specific and diffuse effects on the CNS, this model may be applicable to drug exposure follow-up studies.

Although IVH appears to be a well-defined insult, like prenatal cocaine exposure, it does not usually occur in isolation. Neonates who develop IVH tend to have many other complications of prematurity, especially developmental breathing problems such as respiratory distress syndrome and apnea. These problems may independently affect brain development. Therefore, we have included another measure of biological insult, the number of other common complications of prematurity, along with IVH severity, in our analytic model. As developmental outcome clearly is associated with environmental conditions, and as IVH covaries somewhat with socioeconomic status (SES) due to the mutual association of these variables with low birth weight, measures of environmental
risk also have been included in our model (Bendersky & Lewis, 1994; Lewis & Bendersky, 1989).

Thus, we have embraced a model of development of these high-risk infants, applicable to the cocaine-exposed infant, which acknowledges the potential impact of other biological and environmental risk factors even in the face of a relatively specific medical complication. Moreover, our use of a variety of developmental outcomes at different ages allows us to see what outcomes may be related to IVH alone, those related to other biological insults, poor parenting or low SES, and those related to the interaction of these factors. Analyses of attentional, motoric, sensorimotor, language, and abstract visual reasoning abilities over the age span 3 months to 3 years, have produced a fairly cohesive picture of the specific effects of IVH (Bendersky & Lewis, 1991, 1994; Lewis & Bendersky, 1989). It appears that by 3 years of age, IVH itself has sequelae limited to the motor system when the effects of more general medical condition at birth and the family environment are controlled. It is primarily children who had associated white matter lesions who continue to have motor problems.

Figure 9.1 illustrates the amount of variance explained by each of the three types of predictor variables—IVH, general medical condition, and environmental risk—on language, abstract and visual reasoning, and quantitative and motor skill at 3 years of age. IVH primarily explained some of the variance in the motor and language abilities, and the number of other medical complications suffered during the neonatal period (Medical Complications Score; MCS) explained variance in motor, language, and abstract and visual reasoning skills. The environment explained the most variance in language and quantitative ability. It is clear that the independent effects of IVH are very circumscribed. The cumulative impact of other medical complications of prematurity and environmental risk surpass the specific effect of IVH on developmental consequences.

FIG. 9.1. Variance explained in 3-year outcome measures by IVH, general medical condition, and environmental risk.
These findings have several implications generalizable to the study of effects of prenatal drug exposure. First, it is important to have measures of other prenatal or neonatal conditions that may have similar developmental effects. In the case of substance abuse, such variables as exposure to nicotine, prenatal nutrition, exposure to disease organisms, or medical complications of prematurity should be controlled when looking for specific drug exposure effects. Second, postnatal environmental factors must be controlled, lest they become hidden, confounding variables that themselves alone explain the variability in developmental outcome. In this case, outcome differences may be falsely attributed to prenatal drug exposure because drug use is associated with suboptimal environmental conditions. Third, multiple, specific outcomes, related if possible to theoretically predicted functional deficits, must be assessed in order to understand the specific effects of drug exposure, as well as to shed light on the mechanisms of effect.

Having rejected IQ, what kinds of measures of functioning of cocaine-exposed children should we use? Ideally, they should measure specific functions, have a theoretical connection with prenatal cocaine exposure, have long-term functional significance, and have a reliable test procedure. Such capacities as attention, learning, memory, emotional responsivity, and regulation appear to be appropriate areas of inquiry.

Our laboratory has used contingency learning and its emotional concomitants to study early cognitive development in normal samples of infants. We have begun to apply this methodology to the study of the effects of prenatal cocaine exposure as an appropriate alternative to more global measures of function.

**LEARNING AND EMOTION AS MEASURES OF INFANT FUNCTIONING**

Unlike standardized infant development assessment instruments that measure attainment of developmental milestones and show very poor predictive validity, contingency learning is a measure of the fundamental ability to associate a voluntary behavior with its consequence. Our procedure is language free, requires minimal motor control, and is self-motivating. Moreover, studies of learning in rats have suggested that there is a specific effect of cocaine exposure on brain mechanisms for learning and reward (Heyser, Chen, Miller, Spear, & Spear, 1990; Heyser, Spear, & Spear, 1992; Spear, Kirstein, & Frambes, 1989; Spear et al., 1989). These studies suggest that early learning and accompanying affective responses may be critical functions on which prenatal cocaine exposure has specific effects.

Learning procedures are particularly appealing as measures of infant information processing. They not only tap the subject's ability to form expected associations, but also can be readily employed to study the development and maintenance of motivational systems. They have been used for this purpose in the animal literature for decades. Some of the classic animal paradigms have served
as models for human motivational systems. For example, the phenomenon of learned helplessness originated in the animal literature and has found application as a model of depression in the human clinical literature.

Apart from a few early studies of conditioned fear (Watson & Rayner, 1920) and smiling (Brackbill, 1958), the study of learning and emotion proceeded independently in infant research. With the advent of video technology and the development of coding systems for emotion based on facial musculature, more objective coding of infant facial expression is possible (Ekman & Oster, 1979; Izzard, 1983). We now have the opportunity to combine traditional learning methods with a very untraditional and uniquely human measure, human facial expression. Before describing our work with cocaine-exposed infants we review the procedures and data on learning and emotion developed in our laboratory.

To study learning in young infants, we use pulling or arm retraction as the target response. Infants between the ages of 2 and 8 months are seated in an infant seat in the apparatus and a ribbon connected to a microswitch is attached to their wrists (see Fig. 9.2). Infants typically do not reach toward and grasp objects until the fourth to fifth month of life. Before this time, however, gross movements of the arm are frequent during infant play activity. Sensitive microswitches, mounted so as to register movement toward the infant's body, record pulls automatically. The need to grasp is avoided by having infants wear an elastic wristlet, which fits snugly and allows the ribbon to be quickly and easily connected to the baby's wrist. Ribbon tension is set so that hand-to-mouth activity alone will not trigger stimulus onset.

Pulling the ribbon produces a colored slide of a smiling infant and a few bars of the Sesame Street theme for 3 sec. The stimulus comes on every time the

FIG. 9.2. An infant seated in the contingency apparatus, pulling to trigger a burst of slides and music.
string is pulled. Multiple responses occurring within the 3-sec reinforcement window do not prolong the period of stimulation but are registered. (Further details about the test apparatus can be found in Lewis, Sullivan, & Brooks-Gunn, 1985.)

In our initial investigations, we reported that infants found the procedure interesting and were willing to remain in the experimental apparatus for a considerable length of time provided they controlled the stimulus. Figure 9.3 tracks subject loss during testing over time. Subjects were removed from the apparatus if they cried continuously for 60 sec, dozed for 60 sec, or were inactive for 2.5 min. The graph contrasts time remaining in the experiment for a group of infants who received the contingency (contingent) and a group of control infants who received matched rates of the slide–music presentation independent of their pulling (noncontingent). The figure shows that in the noncontingent group, subjects began to drop out of the experiment quite dramatically after 4 min, whereas loss from the contingent group was more gradual and exceeded 10% only after 10 min. The longest time logged by a noncontingent subject was 20 min; the longest time recorded by a contingent subject who remained active and awake throughout this time was 36 min. Presumably, this difference in motivation occurs because infants in the contingent group have learned to control the outcome, whereas the noncontingent group has not.

The major age-related difference in responding, replicated now in several studies, is that older infants pull at greater rates because they are stronger, better

![Pulling Over Minutes](image)

**Fig. 9.3.** Subject loss under conditions of either contingent or noncontingent presentation of slides and music. The graph shows the number of subjects completing 3-minute intervals in the apparatus without fussing.
coordinated and more active. It is also the case that the response curves of contingent and noncontingent infants diverge later in the procedure for the 2-month-old infants than for the older age groups. However, it appears that the infants learn that they control the stimulus within 3 to 4 min at all ages studied (Lewis et al., 1985).

In order to study the motivational system as well as learning ability, we simultaneously videotape full-face close-ups of the infants as they respond in the procedure. These tapes are subsequently coded using the Maximal Discriminative Facial Coding System for Infants and Young Children (MAX; Izard, 1983). In brief, the system allows for independent coding of changes in facial musculature in each of three regions of the face (brows, eye/cheek, and mouth). MAX formulas are then used to objectively determine which distinctive facial expression or blend has occurred.

Figure 9.4 shows the different positive facial expressions commonly observed in our work. Each of these expressions is usually observed during learning. They are from left to right: excited interest, enjoyment, and surprise.

Because we are interested in points of change during learning, we initially examined individual learning curves to determine how to best sample emotion. Figure 9.5 shows a learning curve produced by a 6-month-old infant in our procedure. The response curve of an infant of the same age and gender is also shown. This infant received the same amount of stimulation, but it was not related to his arm movements. Despite individual differences in response rate, the learning curves of infants in our study shared several characteristics that are nicely illustrated in the contingent subject’s curve. First, infants typically show a period early in the learning session (Point 2) when responding is at, or may fall below, baseline (designated Point 1), as shown by Point 2. This is followed by a rapid acceleration of response (Points 3 and 4), a period of maximally elevated responding (Points 5, 6, and 7) and a period of decline (Point 8). Finally, the baby’s level of response typically returns to baseline levels (Point 9). The operational definitions for each of these points are provided in the figure legend. Each of these points could be identified in learning curves across all infant age groups. These points during the procedure were then coded for infant facial
expression. Our hypothesis was that emotions would vary across these selected points because response rates, and presumably attendant cognitions, were changing, and that maximum enjoyment was likely to co-occur with the peak response—a sign of contingency mastery. The data for 4- and 6-month-olds, described by Sullivan and Lewis (1989) are summarized briefly here. All expressions observed (interest, surprise, enjoyment, sadness, fear, and anger) showed significant changes across the phases of the learning curves. The patterns, with the exception of one expression (anger), were similar.

For purposes of discussion, the 6-month data are presented in Fig. 9.6. Interest and surprise are greatest before the peak response and decline gradually thereafter. Enjoyment occurs at its greatest levels at the point of peak responding. All positive expressions have declined by the final minute when pull responses have also declined. Negative expressions occur rarely across all minutes when the infant is engaged in the task, but increase as pulling declines, presumably because of fatigue or boredom. Fear, expressed predominantly as fear/interest blends, and some sadness, occur at low levels prior to or early in the acceleration phase. The infant may not as yet understand the contingency at this early stage in learning and may be startled by its onset, hence the expression of some negative emotion.
A. Positive Expressions over Selected Points in the Learning Curve

B. Negative Expressions over Selected Points in the Learning Curve

FIG. 9.6. Positive and negative facial expressions (MAX-coded) of 24-week-olds (n = 10) observed during particular phases of the learning curve.

In more recent work, we have examined negative expressions in greater detail by studying infants’ emotional responses when the expected contingency between pull response and interesting outcome is stopped (Alessandri, Sullivan, & Lewis, 1990; Lewis, Alessandri, & Sullivan, 1990; Sullivan, Lewis, & Alessandri, 1992). After a short training period in which infants meet a learning criterion, the contingency is interrupted for 2 minutes. The slide and music will not turn on during this period (extinction). Thereafter the contingency is reinstated. The data from several investigations have consistently shown that pull responses increase during this period, as the infant initially attempts to reinstate the contingency. Figure 9.7 shows data for a group of subjects who persisted through two extinction and two relearning periods. Pull responses increase in rate during extinction, return to the level of the initial contingent phase with the restoration of the contingency, and increase again during the second extinction phase.

The emotional responsivity of infants during extinction is also of interest. Frustration in response to the inability to turn on the stimulus can be expected to produce an increase in negative affect. But the pattern of facial expressions is telling. Anger, but not other negative expressions, increases significantly (Lewis et al., 1990; Sullivan et al., 1992). Figure 9.8 shows this effect for the contingent and the noncontingent control groups. Noncontingent subjects show little anger as can be seen in the figure. For contingent subjects, the increase in anger during extinction is seen at every age, although the number of anger expressions is greater in older subjects. Joy, as measured by infant smiling, shows exactly the opposite pattern. It is high during periods of contingency, and absent during extinction (see Lewis et al., 1990, for further discussion of these data).

Our work shows that contingency learning procedures offer a window not only on the information processing abilities of the young infant, but also on
Pulling Over Learning Phases

FIG. 9.7. Increases in pulling observed in 4-8-month-old subjects exposed to multiple alternating blocks of either contingent or noncontingent stimulation (L1, LII, LIII) and extinction (EI, EII).

Anger Expressions During Learning and Extinction

FIG. 9.8. Expressions of anger observed during learning and extinction at each of four ages.
emerging motivational systems. Responses to frustration are readily studied during periods of extinction or whenever a learned expectancy is violated.

LEARNING AND EMOTION IN COCAINE-EXPOSED INFANTS: A PILOT STUDY

The extensive experience of our laboratory using this contingency learning method with samples of normal infants permitted us to apply it to the question of whether in utero cocaine exposure has an impact on early learning and its emotional concomitants in humans. A sample of 72 4- to 8-month-old infants, half of whom had been prenatally exposed to cocaine, were studied. The procedure was identical to that used in our previous studies. The rates of pulling, frequency of each emotional expression, and amount of fretting during Baseline, Learning 1, Extinction, and Learning 2 were compared for the two groups of infants—exposed and unexposed. (For a complete description of method and results see Alessandri, Sullivan, Imaizumi, & Lewis, 1993.)

Figure 9.9 displays the pull responses for each phase as a function of cocaine exposure group. There were three major differences in the contingency learning of the infants exposed to cocaine compared with their unexposed counterparts. First, the infants exposed to cocaine showed less overall activity, as evidenced by a lower rate of pulling over the entire procedure. Second, although the groups did not differ in pulling during Baseline and Learning 1, the exposed infants did not show the expected increase in pulling during the Extinction period. Finally, the unexposed subjects decreased their response rate when the contingency was reinstated (Learning 2) to a level similar to that during Learning 1. The exposed subjects, however, decreased their pulling to the baseline level. This last finding suggests that cocaine-exposed infants were unmotivated to continue exploring the contingent outcome. After mild frustration, they simply gave up.

![Pulling over Experimental Phases](image)

FIG. 9.9. Rates of pulling by cocaine-exposed and unexposed infants during learning and extinction.
The emotion results parallel the learning findings. Figure 9.10 presents the frequencies of positive emotional expressions (i.e., interest and enjoyment) and anger expressions for each phase as a function of exposure group. There were fewer positive and negative expressions overall in the cocaine-exposed group. Exposed infants showed significantly less interest and joy during the initial learning phase compared with the nonexposed subjects. Moreover, there were fewer negative emotional behaviors when the machine stopped “paying off” (extinction). The predominant negative expression observed during extinction was anger. Sad expressions occurred with low frequency during extinction in the unexposed group, replicating our earlier results for normal infants (Lewis et al., 1990). Sad expressions were virtually absent in the exposed group, which in addition, showed significantly less fussing than the control group over the entire procedure.

A. Positive Expressions

B. Anger Expressions

FIG. 9.10. Frequencies of total positive expressions and anger by cocaine-exposed and unexposed infants during learning and extinction.
Given the possible confounding effects of compromised infant health status and exposure to other potentially harmful substances in utero on learning behavior, analyses were conducted to control for newborn growth characteristics and maternal use of alcohol and cigarettes during pregnancy. The results indicated that cocaine exposure group was the only significant predictor of pull rate and frequency of positive or negative expressions during the different phases of the procedure.

Taken together, the findings for the pulling, facial expressions, and fussing suggest that the cocaine-exposed infants were less engaged by the contingency task. Although their pattern of responses paralleled those of the unexposed subjects, the cocaine-exposed infants were much less aroused. Problems with arousal may represent an underlying difficulty with sustained sensory processing and may be related to childhood hyperactivity or learning disabilities at school age (Doyle, 1975). Moreover, an increase in expressions of joy when a problem is mastered is thought to reflect an infant's active cognitive engagement and a sense of efficacy (Lewis et al., 1990; Lewis & Goldberg, 1969; Piaget, 1952; Sullivan & Lewis, 1989; Watson, 1972; White, 1959). Its absence in the exposed group suggests that these infants are unchallenged or unrewarded by the contingency. Finally, the lack of a vigorous reaction to the discontinuation of the contingency, and the failure to respond when the contingency is reinstated, corroborates this lack of motivation to persevere in the face of obstacles. This may be a pattern that places children at risk of failing to develop feelings of competency and mastery motivation (Lewis & Goldberg, 1969; White, 1959).

The lack of emotional responsivity in cocaine-exposed infants has implications for social development as well. Mother-infant interactions are generally characterized by synchronous behavior that results in mutually optimal stimulation levels (Brazelton, Koslowski, & Main, 1974; Stern, 1974). Our results suggest this contingency, reciprocity, and synchrony may be problematic for cocaine-exposed infants. Given the low level of arousal and lack of emotional responsivity seen in response to a contingency that normally is quite enjoyable for young infants, we think that exposed infants may respond with similarly flat affect to the social contingencies present in parent-child interactions. If so, the caregiving relationship may be unsatisfying for the parent. Caregivers of cocaine-exposed infants may be less successful in maintaining the infants' attention and arousal. They also may have difficulty eliciting affective behaviors such as smiles and coos that are necessary for continued engagement (Osofsky, 1976; Osofsky & Danzger, 1974). Furthermore, the feelings of frustration and inadequacy that parents may experience in dealing with apparently unresponsive infants may predispose them to child maltreatment, as has been seen in other high-risk infant groups (Garbarino & Gilliam, 1981).

The results of this preliminary study indicate that cocaine exposure during gestation may specifically influence arousal, engagement in a contingency task, and emotional responsivity in the first year of life. Further study of discrete
domains of infant functioning, such as attention, learning, memory, emotional responsivity, and regulation, may be the most fruitful approach to understanding specific problems associated with in utero cocaine exposure.

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