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Neuropsychologic Function in Toddlers Exposed to Cocaine In Utero: A Preliminary Study

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Patterns of neuropsychological performance on A-not-B, inhibition, motor, cognitive, language, and behavior tasks were examined in 34 toddlers—17 cocaine-exposed (CE) and 17 nonexposed (NE) controls. CE toddlers exhibited greater perseveration, less inhibition, poorer emotional regulation, and less task orientation relative to NE toddlers. Overall cognitive and language skills and motor impairment status were comparable among CE and NE toddlers. Differences in perseveration, emotional regulation, and task orientation between CE and NE toddlers remained significant after statistically controlling for overall cognitive skill. Prenatal cocaine exposure may impart selective vulnerability for deficits in executive function, inhibition, and emotional regulation in toddlers, perhaps related to the concurrent rapid frontal lobe maturation and the neurobiology of cocaine. Furthermore, these findings suggest that performance can be broken down into meaningful neuropsychological components in very young children.

Approximately 0.4 to 20% of infants are exposed to cocaine during gestation (Chasnoff, Landress, & Barrett, 1990; Frank et al., 1988). Cocaine is a small, low-weight, lipid soluble molecule that easily crosses the placental and blood-brain barriers by simple diffusion. The fetus incurs greater exposure to cocaine than that administered exogenously to the mother (Woods, Plessinger, & Clark, 1987), because the metabolizing agent in the liver and blood is reduced in the fetus and pregnant women (Stewart, Inaba, & Lucassen, 1979). Cocaine acts as a sympathomimetic centrally by blocking the presynaptic reuptake of catecholamines, most notably dopamine, distributed predominantly in the striatal, mesolimbic, and mesocortical brain regions. Long-term cocaine use has been linked to chronic dopamine depletion (Dackis & Gold, 1985), down regulation of receptor binding sites (Wang & Schnoll, 1987), and changes in glucose metabolism (Dow-Edwards, 1989). Cocaine also produces vasoconstriction, which is especially detrimental for the fetus, because appropriate development depends on adequate placental blood flow to provide nutrition and oxygen (Moore, Sorg, Miller, Key, & Resnick, 1986). Reduced blood flow produces fetal ischemia and hypoxia that independently compromise neuropsychological function.

Several studies have examined the neurobehavioral consequences of prenatal cocaine exposure in both full-term and preterm infants (e.g., Chasnoff, Burns, Schnoll, & Burns, 1985; Espy, Riese, & Francis, 1997). In general, compromised state regulation and stimulus orientation and alterations in motor tone have been noted, although not all studies find similar results. Several large-scale investigations are now underway examining developmental outcome in cocaine-exposed (CE) children. These studies have not found differences in overall mental and psychomotor skills among toddler and preschool CE, other-drug-exposed, and nonexposed (NE) children (e.g., Griffith, Azuma, & Chasnoff, 1994; Hurt et al., 1995). Only a few studies conducted to date have used neuropsychologic tasks. CE preschoolers showed less sustained attention and poorer verbal and memory skills (Rodning, Beckwith, & Howard, 1989). Relative to NE controls, CE children had less representational play and compliance, fewer positive social interactions, more irritability, and altered attachment relations (Beckwith, Crawford, Moore, & Howard, 1995). Interestingly, response inhibition during a delay and maternal temperament ratings were comparable among CE and NE preschoolers (Beckwith et al., 1995). Griffith et al. (1994) found that prenatal cocaine exposure was associated with deficits in verbal reasoning, although the magnitude of the effect was less than the standard error of the measure. These findings suggest that CE children may exhibit adequate overall cognitive skills with specific neuropsychologic impairments.

Within developmental neuropsychology, interest has burgeoned recently in the development of executive abilities and the presumed corresponding role of the frontal lobes. Goldman (1974) demonstrated elegantly the link between frontal lobe function and delayed response performance through various experimental

manipulations that permanently alter (Goldman & Rosvold, 1972) or reversibly disrupt (Alexander & Goldman, 1978) frontal lobe function. The frontal lobes have rich connections to dopaminergic subcortical structures such as the basal ganglia. Pharmacological administration of dopaminergic antagonists and agonists also results in respective decrements and enhancements in delayed response performance (Arnsten & Goldman-Rakic, 1985). Altered dopaminergic neurotransmitter function, indicated by reduced homovanillic acid concentrations in cerebrospinal fluid, was found in human CE neonates (Needman, Zuckerman, Anderson, Mirochnik, & Cohen, 1993). Investigating executive function in young CE children permits examination of the relation between executive function and such neurochemical changes.

Diamond (1985) successfully applied delayed response paradigms from these neuroscientific studies with animals to human infants with the A-not-B task (AB; Diamond & Goldman-Rakic, 1989). Similar performance, that is, continuing to search at the previously rewarded location, was observed in frontally ablated adult monkeys (Diamond & Goldman-Rakic), neurologically intact infant and frontally ablated infant monkeys (Diamond, 1990), and neurologically intact human infants (Diamond, 1985). On the basis of these findings, Diamond (1988) concluded that infant AB performance is due to frontal lobe immaturity. Fox and Bell (1990) substantiated these conclusions with electrophysiologic methods. They found that infants who were successful on AB had increased frontal alpha electroencephalogram (EEG) activity and greater coherence between frontal and parietal sites relative to unsuccessful infants.

Executive functions have been investigated in infants and older children but not in toddlers (12–36 months of age). Toddlerhood represents a critical period in frontal lobe maturation concurrent with a growth spurt in coherence in resting EEG recordings (Thatcher, 1991), the achievement of maximal synaptic density (Huttenlocher, 1979), and the beginning of large-scale synaptic pruning (Rakic, 1991). Goldman (1974), in her work with primates, demonstrated that alterations in behavior from neurochemical brain changes depend on the developmental sequence by which differing brain areas subsume different cognitive functions with maturation. Executive functions may be vulnerable to disruption during this developmental period because of the rapid frontal lobe maturation. Toddlers who have been exposed in utero to cocaine, with concomitant dopaminergic-frontal lobe dysfunction, may be prone to display executive deficits.

The first goal of this study was to examine the effect of prenatal cocaine exposure on a range of neuropsychologic tasks in toddlers. The secondary aim was to investigate the specific effects of in utero cocaine exposure on executive functions. CE toddlers were hypothesized to exhibit particular deficits on AB, inhibition, and motor tasks, given the relation of these tasks with frontal lobe function (Welsh & Pennington, 1988). Few, if any, differences were expected relative to NE controls on tasks assessing overall cognitive skills.

METHOD

Participants

Thirty-four toddlers between 17 and 21 months of age ($n = 17$ CE toddlers; $n = 17$ NE controls) participated. CE toddlers were recruited from “graduates” of an outpatient drug-treatment facility in the southwestern United States, specifically designed to provide substance abuse treatment for pregnant and postpartum women, including prenatal care. Graduate status entailed continuous maternal participation in the program for at least 15 months and reported abstinence from use of any illicit substance for the 12 months preceding study recruitment. Only two women declined participation.

Maternal prenatal drug use information was provided perinatally by the mother to the intake counselor at the drug abuse treatment program either just prior to the child’s birth ($n = 10$) or within 3 months of delivery ($n = 7$). The primary illicit drug of abuse of the majority of women was cocaine; however, women also reported use of other substances. Sample maternal drug use characteristics are depicted in Table 1. Seventy percent of the CE toddlers were exposed in utero to alcohol or to tobacco in addition to cocaine, which is similar to percentages reported in other investigations with drug-using women.

NE toddlers were recruited from birth announcements published in the local newspaper and from a local nursery school. Participants were included only if the mother denied any use of alcohol, tobacco, or illegal or prescription drugs during pregnancy. For this preliminary study, a low-risk control group was recruited to determine any differences related to prenatal exposure relative to an “average” child.

Sample demographic characteristics also are provided in Table 1. First, the NE group contained more boys than the CE group, $\chi^2(1, N = 34) = 4.64, p < .05$. The groups also differed with respect to the number of infants of minority ethnicity, $\chi^2(1, N = 34) = 4.64, p < .05$. The NE group was predominantly White, whereas the CE group contained more toddlers of minority ethnicity, with Hispanic being the most common. There were, however, no performance differences on any of the outcome measures due to sex or ethnicity. The groups also differed with respect to mean age, $F(1, 32) = 16.32, p < .01$. The age difference was due to appointment cancellations on the part of controls. The age difference was small (about a month) and the age range of the two groups was equivalent (NE: 17.1–21.6 months; CE 17.5–20.5 months).

Measures

Toddlers were administered a neuropsychological battery of standardized and experimental measures evaluating general cognitive, language, behavior, and executive function, inhibition, and motor skills. General cognitive skills were assessed by

TABLE 1
Sample Demographics by Group Membership

<i>Characteristic</i>	<i>Nonexposed^a</i>	<i>Cocaine-Exposed^b</i>
Sex*		
Men	1	8
Women	3	9
Race*		
White	4	8
Minority	3	9
Term		
Full-term	16	15
Pre-term	0	2
Prenatal drug exposure		
Cocaine	0	17
Amphetamine	0	3
Opiate	0	1
Marijuana	0	3
Alcohol	0	12
Tobacco	0	14
Age (months)**		
<i>M</i>	20.0	18.6
<i>SD</i>	1.3	0.8
Maternal age ^b (years)		
<i>M</i>	31.3	28.0
<i>SD</i>	5.6	6.0
Birthweight ^c (kg)		
<i>M</i>	3.5	3.1
<i>SD</i>	0.5	0.5

^a*n* = 17. ^b*n* = 16, nonexposed group. ^c*n* = 15, nonexposed group and *n* = 14, cocaine-exposed group.

p* < .05. *p* < .01.

the Mental Development Index (MDI) from the Bayley Scales of Infant Development, 2nd edition (BSID; Bayley, 1993). Behavior skills were measured by the Orientation and Engagement (OE) and Emotional Regulation (ER) subscales from the BSID Behavior Rating scale (Bayley, 1993). The examiner rated the child's behavior during the test session (e.g., positive affect, task attention, hyperactivity) on a 4- or 5-point scale. Unlike the MDI, which is a standard score, the behavioral scores are percentile scores. Motor impairment was scored dichotomously from the Motor subscale from BSID Behavior Rating scale (Bayley, 1993), with impairment defined as any score below the maximal score of 40. Language skills were assessed with two scales from the Preschool Language Scale-3 (Zimmerman, Steiner, & Pond, 1992): Auditory Comprehension (AC) and Expressive Communication (EC).

Executive function was assessed by the AB task (Diamond, 1985). The toddler watched a reward hidden in one of two wells. After a 5-sec delay (where the examiner counted aloud as a distraction), the toddler retrieved the reward. A 5-sec delay was used, because pilot testing indicated that toddlers did not remain in their seat with longer delays. The reward location changed after the child correctly retrieved the reward for 2 consecutive trials on the same side. A total of 10 trials were administered. The dependent measures were *perseverative errors*, the number of trials that the toddler erred by retrieving the reward at the incorrect location after having searched correctly at the alternate location; *perseverative runs*, the maximal number of trials in a given set of consecutive perseverative errors; and *number of sets achieved*, the number of times the child correctly retrieved the reward for two consecutive trials.

The inhibition task was modeled after a self-control task devised by Vaughn, Kopp, and Krakow (1984). First, the child's interest in a reward was generated through animated verbalization. There were two trials; the first trial utilized food as the reward, and the second trial, a wrapped gift. The examiner instructed the child not to touch the reward while the examiner completed another task where no attention was given to the child (e.g., the examiner scored other tasks on the battery). It was scored on a pass-fail basis if the toddler inhibited touching the reward for 150 sec on either trial.

Procedure

Toddlers were administered the neuropsychological battery in a single testing session, approximately 75 min in length. Toddlers were tested at a time convenient to scheduled naps and feedings. Breaks were administered as necessary to maintain cooperation and interest. The evaluators were not blind to cocaine-exposure status. Prior clinical experience within this population indicated that drug-using families had significant difficulty meeting scheduled appointments at unfamiliar locations. To minimize ascertainment bias, CE toddlers were evaluated at the drug-treatment facility where their mothers' had been receiving services for the past 15 months. The NE toddlers, however, could not be evaluated at the drug treatment facility, because agency insurance covered only patients. NE toddlers were assessed at the university medical center, precluding blind evaluations.

RESULTS

Three one-way multivariate analyses of variance (MANOVAs) were conducted on conceptually related measures: one for the executive function measures, one for the general cognitive and language measures, and one for the behavioral measures. One-way analyses of variance (ANOVAs) for each dependent variable were examined when the overall MANOVA was significant. CE and NE groups differed on

AB, Wilks's $\lambda = 0.72$, $F(3, 30) = 3.84$, $p = .02$. Results from the one-way ANOVA analyses of group differences on each dependent variable are presented in Table 2. CE and NE groups differed in AB perseverative errors, perseverative runs, and the number of sets achieved. Mean task performance by group is depicted in Table 3. On average, the CE group committed 4.00 perseverative errors, with 3.18 errors in the longest run. The NE group made fewer perseverative errors, perseverated consecutively across fewer trials, and achieved a mean of one more correct two-trial set than CE toddlers.

TABLE 2
AB, Cognitive, Language, and Behavior Task Performance by Group

Task	Nonexposed ^a			Cocaine-Exposed ^a		
	M	SD	Range	M	SD	Range
AB errors	2.35	1.62	0.0-4.0	4.24	1.71	2.0-7.0
AB runs	1.59	1.28	0.0-4.0	3.35	1.80	1.0-7.0
AB sets	3.47	1.28	1.0-5.0	2.47	1.07	1.0-4.0
MDI	106.18	12.06	82.0-124.0	93.76	13.02	69.0-111.0
AC ^b	102.00	11.80	84.0-123.0	93.14	11.38	81.0-119.0
EC ^b	100.00	18.99	77.0-130.0	90.00	12.08	74.0-112.0
ER	90.29	15.30	43.0-99.0	58.06	30.19	7.0-98.0
OE	90.53	15.98	46.0-99.0	55.41	33.01	1.0-99.0

Note. AB = A-not-B task; MDI = Mental Development Index; AC = Auditory Comprehension; EC = Expressive Communication; ER = Emotional Regulation; OE = Orientation Engagement.

^a $n = 17$. ^b $n = 12$, nonexposed group and $n = 14$, cocaine-exposed group.

TABLE 3
Results of Task Performance Differences Between Cocaine-Exposed and Nonexposed Toddlers With and Without Controlling for Cognitive Level

Measure	ANOVA		MDI Controlled ANOVA	
	df	F	df	F
AB errors	1, 32	10.84**	2, 31	5.30*
AB runs	1, 32	10.86**	2, 31	6.10**
AB sets	1, 32	6.12*	2, 31	2.43
ER	1, 32	15.42**	2, 31	6.08*
OE	1, 32	15.59**	2, 31	6.33*

Note. ANOVA = analysis of variance; MDI = Mental Development Index; AB = A-not-B task; ER = Emotional Regulation, OE = Orientation Engagement. These analyses were not reported for the cognitive and language measures, because the overall multivariate analysis of variance was not significant, obviating further exploration of any group differences.

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

There was no significant difference between groups in overall cognitive and language skills, Wilks's $\lambda = 0.81$, $F(3, 22) = 1.72$, $p = .20$. In Table 3, performance for both groups was in the average range although CE toddlers performed somewhat more poorly. Behavior skills, in contrast, differed among CE and NE groups, Wilks's $\lambda = 0.62$, $F(2, 31) = 9.68$, $p < .01$. Examiner ratings of both ER and OE skills differed among CE and NE toddlers. As reported in Table 3, CE toddlers were rated as less well regulated and less engaged during the testing session than NE controls, although mean behavior of both groups was rated as within normal limits. Behavior of the CE group was more variable than that of the NE toddlers. The majority of the NE toddlers performed at or near the ceiling of the rating scales.

Chi-square analyses (2×2) were conducted on the dichotomously coded variables. Results for the inhibition and motor tasks are depicted in Table 4. On the inhibition task, there were significantly fewer CE toddlers who inhibited touching the reward on either trial, $\chi^2(1, N = 34) = 4.50$, $p = .03$. There was no difference in the number of children who evidenced motor impairment, $\chi^2(1, N = 34) = 0.37$, $p = .55$.

The executive function and behavioral measures also were analyzed, controlling for the influence of cognitive level (analysis of covariance), to examine whether group differences in executive skill and behavior exceeded what would be expected on the basis of overall MDI score. Significant group differences in perseverative errors and runs remained after partialing the MDI score; CE toddlers made more perseverative errors and perseverated across more consecutive trials than NE toddlers (see Table 3). Like AB error indexes, mean ER and OE percentiles continued to differ among CE and NE toddlers after removing the effect of cognitive level. However, the MDI score accounted for significant variability in the behavioral measures. The mean semipartial percentile scores were 83.87 and 64.48 for NE and CE toddlers, respectively. The magnitude of the change in OE mean percentile was similar to that for ER. In contrast, differences in the number of AB sets achieved was no longer significant after partialing cognitive level. The mean number of sets achieved by the CE group was reduced to 2.62 and 3.31 for the NE group.

TABLE 4
Inhibition and Motor Results by Group

<i>Measure</i>	<i>Nonexposed^a</i>	<i>Cocaine-Exposed^a</i>
Inhibition*		
Inhibited	6	1
Impulsive	11	16
Motor impairment		
Normal	16	15
Impaired	1	2

^a*n* = 17.

**p* < .05.

DISCUSSION

CE toddlers showed distinct, identifiable neuropsychological performance patterns. First, CE toddlers exhibited specific deficits on AB. The CE group, on average, made more perseverative errors and perseverated consecutively across more trials than NE controls. Second, fewer CE toddlers inhibited touching a reward during the delay. These findings are in contrast to those of Beckwith et al. (1995), who found no differences in inhibition on a similar cookie reward task. These discordant results may be related to differences in internal motivation of the rewards. Two rewards were utilized in this study because of potential individual differences in perceived salience of the rewards (more toddlers inhibited on the gift trial). Gifts certainly produce less physiological drive than food and, therefore, inhibition on this trial may have depended more on cognitive factors, thereby increasing the likelihood of detection of individual differences in inhibition.

CE toddlers also differed behaviorally from NE toddlers. For example, the examiner rated CE toddlers as more affectively flat or more negative with few positive emotional expressions, although performance was within the normal range for both groups. These findings are consistent with those of Beckwith et al. (1995) using laboratory-based behavioral measures. However, these findings must be viewed cautiously because the examiner was not blind to exposure status. In contrast to measures of performance, behavior ratings depend directly on the examiner's perspective and may be more susceptible to bias.

Consistent with other studies (Chasnoff, Griffith, Freier, & Murray, 1992; Hurt et al., 1995), no overall cognitive differences related to in utero cocaine exposure were found. In contrast to other investigations (Beckwith et al., 1995; Griffith et al., 1994), significant group differences in language abilities related to prenatal cocaine exposure were not observed in this study. These discordant findings may be related to the measures chosen to assess language. The Preschool Language Scale (Zimmerman et al., 1992) contains few items per age group. However, the mean group performance on both language scales was in the average range, thereby reducing the likelihood that prenatal cocaine exposure was related to specific language dysfunction. Contrary to prediction, the number of toddlers with motor impairment did not differ between groups. Both CE and NE toddlers performed at the ceiling of the Motor subscale. Subtle differences in motor performance related to frontal lobe dysfunction, such as sequencing (Welsh & Pennington, 1988), would be less likely to be detected.

Differences among CE and NE toddlers on AB errors and behavior were greater than expectations based on overall cognitive skill. These findings are concordant with those of Welsh, Pennington, and Grossier (1991), who examined executive function development in older children. In contrast, the number of AB sets achieved was determined, at least in part, by the toddler's cognitive level. Investigations using the Wisconsin Card Sorting Test in older children (Chelune & Baer,

1986) and in adults (Heaton, 1981) have yielded similar findings (i.e., with the number of categories achieved as the dependent measure). These findings suggest that both perseveration and the number of sets achieved may contribute uniquely to AB performance in toddlers. In contrast, ER and OE behavior was influenced both by CE group status and overall cognitive level.

These results must be considered preliminary for several reasons. First, it is a small sample, comprised of a select clinical group. Toddlers born to drug-using women actively in treatment may differ from toddlers born to mothers who are not in, nor have sought, drug treatment. Because this sample of women reported abstinence for at least the 12 months preceding study recruitment, these families may be higher functioning than those in whom the mother continued to actively use drugs postdelivery. Furthermore, CE and NE groups may have differed in the familial characteristics associated with prenatal drug use (e.g., parenting practices, emotional style, home environment), which may, in turn, impact on executive skills, inhibition, and behavior in toddlers (Mayes & Bornstein, 1995). The relative importance of these familial variables in determining neuropsychological outcome, compared to that of prenatal drug exposure, is unknown. Indirect evidence suggests that executive function may be less affected by familial influences than other skills. Taylor and Schatschneider (1992), in a large sample of postmeningitis children, found that socioeconomic status, home environment, and life stress were unrelated to executive skill. One advantage of sampling women who participated in drug treatment is that treatment entails direct instruction in parenting practices, which, if effective, attenuate these group differences.

Second, NE toddlers were not reportedly exposed to any substances, including legal drugs such as alcohol and tobacco. Self-reported substance use may be biased, as there is a large incentive to deny use. If some of the control children were CE, in fact, the biasing effect would work against the study hypotheses by attenuating any true group differences. CE and NE groups also differed in more ways than just prenatal cocaine exposure. First, most of the CE toddlers were exposed to other substances in utero. Therefore, group performance differences may be attributable to, or are in part related to, other drug exposure. Given the small sample and overlap of other prenatal drug use with cocaine, it was not possible to investigate these effects independently. This sample is representative of the larger population, as polysubstance use is normative among pregnant drug users (Chasnoff et al., 1990). Although children exposed to other substances in utero show cognitive and language decrements (Fried & Watkinson, 1987), the relation between other substance exposure and executive function remains to be investigated. Because other drugs of abuse do not directly affect dopamine to the degree as cocaine (Druse, 1992; Hammer, 1993), such exposed toddlers should not differ in executive skill (Espy & Glisky, 1997). Utilizing a higher risk control group (e.g., matched on tobacco and alcohol exposure) may isolate the unique effects of prenatal cocaine exposure.

These findings are important in light of the neurobiologic effects of prenatal cocaine exposure on dopaminergic brain neurochemistry (Needlman et al., 1993). First, because dopaminergic subcortical structures are connected to the frontal lobes and AB performance has been linked substantively with frontal lobe function, it is not surprising that CE toddlers exhibited executive function deficits on AB. Second, Diamond (1988) proposed that working memory and the inhibition of a prepotent response underlie AB performance. In this study, CE toddlers also were less likely to inhibit responding during a delay. Taken together, these findings suggest that prenatal cocaine exposure may be related to deficits in working memory, inhibition, or both, although the study design does not address whether in utero cocaine exposure affects both or just one of these cognitive components. Third, CE toddlers showed poorer ER and OE skills relative to NE controls. Interestingly, Fox (1994) linked emotional regulation to frontal lobe function in infants, suggesting that approach and activity are related to hemispheric laterality and resting frontal EEG activation patterns, respectively. Whether differences in AB, inhibition, and behavior observed in the CE infants in this study are related to frontal dysfunction is speculative without direct brain measures.

Interest has grown in the neuropsychological development of young children (Welsh et al., 1991) and the impact of neurologic disorder on cognitive development in these children. The findings from this study suggest that application of paradigms from related disciplines are useful to elucidate the neuropsychological consequences of disease and shed light on the process of normal development (Kaufmann, Leckman, & Ort, 1990). Goldman (1974) suggested that developmental time course of the observation of cognitive deficits depends on the underlying maturation of brain structure and function. Cocaine-related deficits may be salient during this developmental period because of critical frontal lobe maturation in toddlers. Longitudinal studies are necessary to determine whether these performance differences persist in later childhood. Studying neuropsychological function longitudinally in young children also provides an opportunity to examine whether selective periods of vulnerability or plasticity in the developing brain exist.

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