Published in final edited form as:

Dev Psychol. 2008 July ; 44(4): 919–928. doi:10.1037/0012-1649.44.4.919.

Children's Cognitive Ability from 4- to 9-Years as a Function of Prenatal Cocaine Exposure, Environmental Risk, and Maternal Verbal Intelligence

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Abstract

This study examined the effects of prenatal cocaine exposure, environmental risk, and maternal verbal intelligence on children's cognitive ability. Gender and age were examined as moderators of potential cocaine exposure effects. The Stanford-Binet IV intelligence test was administered to 231 children (91 cocaine exposed, 140 unexposed) at 4, 6, and 9 years of age. Neonatal medical risk and other prenatal exposures (alcohol, cigarettes, and marijuana) were also examined for their unique effects on child IQ. Mixed models analysis indicated that prenatal cocaine exposure interacted with gender as cocaine exposed boys had lower composite IQ scores. Age of assessment did not moderate this relation, indicating that cocaine exposed boys had lower IQs across this age period. A stimulating home environment and high maternal verbal IQ also predicted higher composite IQ scores. Cocaine exposed boys had lower scores on the Abstract/Visual Reasoning subscale, with trends for lower scores on the Short-term Memory and Verbal Reasoning subscales, as exposure effects were observed across domains. The findings indicate that cocaine exposure continues to place children at risk for mild cognitive deficits into preadolescence. Possible mechanisms for the exposure by gender interaction are discussed.

Keywords

prenatal cocaine exposure; environmental risk; gender differences; intelligence

Prenatal cocaine exposure has been hypothesized to adversely affect children's cognitive development, possibly through its effect on developing neurotransmitter systems critical to neuronal differentiation and brain structure formation (Harvey, 2004; Morrow, Elsworth, & Roth, 2003). More specifically, cocaine has been found to block the reuptake of monoaminergic neurotransmitters, which may disrupt the development of neuronal circuitry in the fetus

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²Values in Figure 1 are based on predicted mean scores for a particular hypothetical individual based on the model coefficients. Values were calculated directly as the inner product of the model coefficient vector and a vector of scores on all of the variables in the model.

(Lidow, 1995; Mayes, 1999). Cocaine exposure also may cause vasoconstriction of cerebral blood vessels, producing a hypoxic condition in the brain that precipitates decreased fetal growth and nutrition (Kurth et al., 1993; van de Bor, Walther, & Sims, 1990). Collectively, these findings suggest that prenatal cocaine exposure is a risk factor for impaired central nervous system (CNS) development, including cognitive ability. Yet, studies of children prenatally exposed to cocaine have yielded inconsistent findings as to whether cocaine exposure affects cognitive ability.

Earlier studies have generally only reported cross sectional data, limiting our understanding of developmental trajectories over time (Mayes, Cicchetti, Acharyya, & Zhang, 2003). Among these studies, several have reported cocaine related cognitive deficits (e.g., Alessandri, Bendersky, & Lewis, 1998; Asanbe & Lockert, 2006; Bennett, Bendersky, & Lewis, 2002; Marques, Pokorni, Long, & Teti, 2007; Singer et al., 2002, 2004), but many have not found cocaine related effects (e.g., Frank et al., 2005; Griffith, Azuma, & Chasnoff, 1994; Hurt, Malmud, Betancourt, Brodsky, & Giannetta, 2001; Morrow et al., 2006; Richardson, Conroy, & Day, 1996; Wasserman et al., 1998). Methodological limitations, including the use of small samples or a failure to control for potential confounds such as prenatal exposure to other substances, environmental risk, and maternal cognitive ability may limit the validity of prior findings.

Longitudinal studies that follow cocaine-exposed children through the elementary school years and beyond are critical for examining the presence of potential sleeper effects (Frank, Augustyn, Knight, Pell, & Zuckerman, 2001; Singer et al., 2004), particularly since brain development continues into early adulthood (Diamond, 2002; Luna, Garver, Lazar, & Sweeney, 2004). As cognitive demands increase, do cocaine-related deficits also increase? Or, do early cocaine-related deficits diminish over time as children develop compensatory skills, or as environmental influences impact cognitive ability? Studies have begun to address the effects of prenatal cocaine exposure on cognitive development over time, though most have been limited to the preschool years. Singer et al. (2002, 2004), for example, found cocaine exposure to be related to global cognitive deficits at 2 years, but only to deficits in specific domains at 4 years (visual-spatial skills, arithmetic skills, and general knowledge). Mayes et al. (2003) found cocaine exposed children to score lower than controls on the Mental Development Index of the Bayley Scales from 3 months to 3 years (Mayes et al., 2003), but did not find the deficits to increase or decrease relative to controls during these early years.

Gender may moderate the relation between prenatal cocaine exposure and child outcomes. In particular, our work and that of others suggests that exposed males, especially if raised in high-risk environments, appear to be at greater risk for inhibitory control problems, emotional modulation difficulties, health risk behaviors, and externalizing problems (Bailey et al., 2005; Bendersky, Bennett, & Lewis, 2005, 2006; Bendersky, Gambini, LaStella, Bennett, & Lewis, 2003; Bennett, Bendersky, & Lewis, 2007; Delaney-Black et al., 2004; Dennis-Tiwary, Bendersky, Ramsay, & Lewis, 2006). While the reasons for such gender specific effects are unclear, they are consistent with research indicating that the male fetus may be more susceptible to intrauterine factors affecting the CNS (Flannery & Liederman, 1994; Hynd & Semrud-Clikeman, 1989; Mathura, 1979; Moe & Slinning, 2001; Montague, 1962; Weinberg, Zimmerberg, & Sonderegger, 1992), although Beeghly et al. (2006) did find girls to be more negatively affected by prenatal cocaine exposure.

Women who use cocaine during pregnancy are much more likely to use other substances also, including alcohol, cigarettes, and marijuana, and to experience environmental risk factors (Bendersky, Alessandri, Gilbert, & Lewis, 1996). Prenatal exposures to these other substances have been associated with poorer cognitive ability (Fried, Watkinson, & Gray, 1998; Korkman, Kettunen, & Autti-Ramo, 2003; Weitzman, Byrd, Aligne, & Moss, 2002). Environmental risk

factors also have been related to poorer cognitive ability. Hurt et al. (2001), for example, found that cocaine-exposed children's lower scores on a developmental inventory at 5-years could be explained by environmental factors in the home environment. Singer et al. (2002, 2004) also found that the quality of the home environment was the strongest predictor of cognitive ability among 2- and 4-year-olds.

While such environmental factors have increasingly been controlled in cocaine exposure research, the examination of important maternal characteristics such as mother's own cognitive ability, which may be impaired among cocaine users (Rosseli & Ardila, 1996), has been rare. A recent exception (Arendt et al., 2004) found cocaine exposed children to have lower IQ scores at 7 years, although the differences became nonsignificant after controlling for mother's vocabulary skills and the quality of the home environment. Maternal characteristics such as low IQ have generally been found to predict poorer intellectual functioning among children in community samples (Burchinal, Campbell, Bryant, Wasik, & Ramey, 1997). Furthermore, research suggests that adult cocaine abusers exhibit mild cognitive deficits (Goldstein et al., 2004), although it is unclear whether such deficits precede or are a consequence of cocaine use. However, to the extent that maternal cognitive ability may serve as a marker for either the child's genetic potential or degree of environmental enrichment, maternal cognitive ability should be controlled, along with the effects of exposure to other substances and general environmental risk, when examining the relation between prenatal cocaine exposure and child cognitive ability.

The purpose of the present study was to examine whether cocaine exposure effects found at age 4 years for boys in the present sample persist at age 6 and 9 years, and whether effects emerge for girls at these later ages. In doing so, we also examined whether there was an age by cocaine exposure interaction; i.e., do the effects of cocaine exposure increase or decrease during the early elementary school-age period? The potential effects of environmental risk, maternal verbal intelligence, gender, prenatal exposure to alcohol, cigarettes, and marijuana, and neonatal health problems were controlled for in examining these questions.

Method

Subjects

The sample of 231 children (120 boys, 111 girls; 39% cocaine exposed) and their mothers were recruited for a longitudinal study on the effects of prenatal exposure to cocaine (see Bendersky & Lewis, 1998). Pregnant women attending participating hospital-based prenatal clinics, or newly delivered women in the three hospitals in Trenton, NJ or at the Medical College of Pennsylvania in Philadelphia were approached. Of these, 82% agreed to participate in the study. Informed consent was obtained at this time. Children were excluded from the study if they were born prior to 32 weeks of gestation, required special care or oxygen therapy for more than 24 hours, exhibited congenital anomalies, were exposed to opiates or phencyclidine in utero, or if their mothers were infected with HIV. Cocaine-exposed children did have shorter gestations than unexposed children (37.8 weeks [$SD = 2.9$] vs. 39.6 weeks [$SD = 1.8$], $t = 4.85$, $p < .001$). Mothers ranged in age from 13.7 to 43.6 years (mean = 25.6; $SD = 6.1$) at the time of birth and were predominantly African-American (87%), with 9% Caucasian and 3% Hispanic. Maternal age was significantly higher among mothers who prenatally used cocaine (28.8 years [$SD = 4.5$] vs. 24.0 years [$SD = 6.1$], $t = 6.45$, $p < .001$). Mothers' median education level was 11th grade ($SD = 1.6$), and 63% of families received Aid to Families with Dependent Children (AFDC). Sixty-one percent of the mothers who used cocaine reported high levels of use (i.e., at least twice per week on average during the pregnancy; Jacobson, Jacobson, Sokol, Martier, & Chiodo, 1996). Among cocaine users, 75% also reported using alcohol, 86% smoked cigarettes, and 31% used marijuana at least once during their pregnancy. Among mothers who did not use cocaine ($n = 118$), 17% reported using alcohol, 23% smoked cigarettes, and 5%

used marijuana. Most children continued to live with a biological parent at the time of the follow-up (86% at age 4 years, 84% at age 9 years); for those subjects residing with someone other than their biological mother, the current primary caregiver completed the measures assessing environmental risk factors (e.g., parental depressive symptoms) for that time point. Participation was voluntary, and incentives were provided in the form of vouchers for use at local stores.

Two hundred eighteen subjects completed the 4 year IQ assessment, 185 completed the 6 year, and 150 completed the 9 year. Subjects who completed all 3 IQ assessments did not differ from those who did not on gender, cocaine exposure, alcohol exposure, cigarette exposure, marijuana exposure, neonatal medical risk, environmental risk, maternal verbal IQ, 6 year IQ, or 9 year IQ scores. However, those who completed all 3 assessments did have higher IQ scores at 4 years than those who did not ($t(216) = 2.67, p < .01$; mean = 86.2 ($sd = 11.1$) for subjects who completed each assessment; mean = 81.9 ($sd = 12.6$) for the others). Multiple imputation, which provides accurate statistical estimates of missing data based on available data (Schafer & Graham, 2002), was conducted with SAS version 9.1 PROC MI under a multivariate normal model to compute missing IQ scores. Data were assumed to be missing at random (MAR) conditional on the observed data, which is ignorable if the MAR assumption is correct. Twenty imputations were conducted (cf. Schafer & Graham, 2002); while one can often achieve substantial efficiency relative to an infinite number of imputations with as few as 5 imputations (Rubin, 1987), estimates are more efficient with a larger number of imputations. Data were combined using SAS PROC MIANALYZE which combines parameter estimates across imputations and provides standard error estimates which take both between and within imputation variability into account. Methods for pooling effects and standard errors across the different imputations are described by Schafer (1997).

Procedure

Children were administered the Stanford-Binet Intelligence Scale (SB-IV; Thorndike, Hagen, & Sattler, 1986) Short-Form at the 4, 6, and 9 year visits by a trained female psychometrist who was blind as to the child's drug exposure status.

Measures of Risk Factors

Environmental and neonatal medical risks—Eighteen environmental and neonatal medical risk factors were reduced via principal components analysis with varimax rotation for use as covariates. A 4-factor solution explaining 45.7% of the variance was retained based on factors having an eigenvalue greater than 1.0 and scree plot analysis. Factor 1 (8 items explaining 16.5% of the variance) consisted of variables related to Environmental Stimulation and included the Academic Stimulation, Learning Stimulation, Language Stimulation, Encouragement of Maturity, Variety in Experience, and Warmth and Acceptance subscales from the Home Observation for Measurement of the Environment (Caldwell & Bradley, 1984), which was administered to mothers during the 4-year lab visit. Factor 1 also included maternal education level (highest grade completed; average of 4- and 7-year scores) and the number of caregivers in the home (average of 4- and 7-year scores).

Factor 2 (3 items; 10.4%), a Maternal Age-related factor, consisted of variables associated with maternal age: maternal age at time of birth, number of prior births, and whether the child's father was in the household (as single mothers tend to be younger; Cairney, Boyle, Lipman, & Racine, 2004) (0=no, 1=yes; mean of age 4- and 7-year scores). Factor 3 (5 items; 9.7%) consisted of variables related primarily to Maternal Stress: negative life events (based on the Social Environment Inventory; Orr, James, & Casper, 1992), maternal depressive symptoms (Beck Depression Inventory; Beck, 1978; average of 4-, 6-, 7-, & 9-year scores), instability of child's surroundings (Family Chaos Scale; R. Seifer, personal communication), child living

with a biological parent (i.e., vs. residing with a kinship care or long-term foster care provider; the mean number of kinship/foster placements at 4- and 7-years), and whether or not the family was on public assistance (Temporary Assistance for Needy Families; average of 4- and 7-year scores). Factor 4 (2 items; 9.1%) consisted of variables related to Neonatal Medical Risk: neonatal medical problems abstracted by nurses from hospital records at the time of birth (Hobel, Hyvarinen, Okada, & Oh, 1973), which was log transformed to correct for significant skew, and gestational age in weeks (reverse scored).

Maternal verbal IQ—The Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn & Dunn, 1981) was administered at the 4 ½ year visit to mothers to provide an estimate of maternal verbal IQ. The PPVT-R correlates highly with the verbal IQ scale of the Wechsler Adult Intelligence Scale (median $r = .71$; Dunn & Dunn, 1981), and the PPVT has previously been used as an estimate of maternal IQ (e.g., Longstreth et al., 1981). The PPVT has been used with African-American adults and has been found to be a valid predictor of IQ for both African- and European-Americans (Dunn & Dunn, 1981; Halpin, Simpson, & Martin, 1990).

Prenatal substance exposure—Substance use information was obtained through a semistructured interview. Interviews were conducted prenatally (65%), in the mother's room on the maternity ward if she had just delivered (30%), in our laboratories near the hospitals (3%), or in the mother's home within 2 weeks of the child's birth (2%). They were administered by trained interviewers and substance abuse counselors. The drug use interview contained questions about the frequency, amount, and trimester use of cocaine, alcohol, cigarettes, marijuana, opiates, PCP, tranquilizers, amphetamines, and barbiturates. Cocaine use was confirmed by results of analysis of newborns' meconium. The infants' meconium samples were screened with radioimmunoassay followed by confirmatory gas chromatography - mass spectrometry for the presence of benzoyl ecgonine (cocaine metabolite), cannabinoids, opiates, amphetamines, and PCP. Mothers showed no signs of PCP, heroin, or methadone use as determined by assay and by self-report in repeated interviews. To reduce skewness of the substance exposure variables, maternal reports were recoded as follows: alcohol (0=0 drinks/day; 1=0.01 to 1.00/day; 2=1.01 to 2.00/day; 3=2.01 to 3.00/day; 4=more than 3/day); cigarettes (0=0 cigarettes/day; 1=0.01 to 1.00/day; 2=1.01 to 5.00/day; 3=5.01 to 10.00/day; 4=more than 10.00/day); and marijuana (0=0 joints/day; 1=0.01 to 0.50/day; 2=0.51 to 1.00/day; 3=more than 1.00/day). The ordinal level alcohol, cigarette, and marijuana use scores were transformed using natural logarithms to further reduce skewness for all analyses other than those in Table 1, which lists the means for maternal substance use prior to recoding and transformation. Cocaine exposure was not recoded but was dichotomized (i.e., into exposed and unexposed groups) in all analyses as prior reports from this sample have found the dichotomous measure to better predict outcomes than more dimensional measures of cocaine exposure (e.g., Bendersky et al., 2006; Bennett et al., 2002, 2007).

Child Cognitive Ability

Stanford-Binet Intelligence Scale, Fourth edition (SB-IV; Thorndike et al., 1986)

—The SB-IV was administered to provide an estimate of general intellectual ability. The subscales of Abstract/Visual Reasoning, Quantitative Reasoning, Short-term Memory, and Verbal Reasoning are summed to produce a composite IQ score. The Short-Form consisted of the Vocabulary, Bead Memory, Quantitative, Sentence Memory, Pattern Analysis, Comprehension, Absurdities, Digit Memory, and Copying subtests. The SB-IV has extensive standardization data and satisfactory reliability, including with African-American children (Krohn & Lamp, 1999; Thorndike et al., 1986).

Results

Group differences between cocaine exposed and unexposed boys and girls were initially examined using analyses of variance (ANOVA). Bivariate correlations between all study variables were then conducted separately by gender to examine whether relations between cocaine exposure and child IQ were greater for boys than for girls. The effect of cocaine exposure and its potential interaction with both gender and child age on IQ, controlling for other risk factors, was examined using a mixed models analysis (Singer & Willett, 2003) with an unstructured covariance matrix for the random effects. To preserve statistical power, any non-significant interaction terms were dropped from the final model except for the cocaine exposure by child age interactions, as the question of whether exposure effects varied by age was a primary study question. Variables used in the final model for the composite IQ were also retained when examining subscales to facilitate comparison between the composite and subscale models.

Table 1 presents means and standard deviations by cocaine exposure and gender for each variable. Cocaine-exposed children had a lower gestational age than unexposed children, and exposed girls had more neonatal medical problems than did unexposed girls as indicated by post-hoc Tukey tests. Mothers of cocaine-exposed children had greater maternal stress and maternal age-related factor scores than did unexposed children. In addition, mothers of cocaine-exposed girls drank more alcohol during pregnancy than mothers of unexposed boys and girls, used more marijuana than mothers of unexposed boys and girls, and smoked more cigarettes than mothers in each of the other three groups. Mothers of cocaine-exposed boys also smoked more cigarettes than mothers of children in the unexposed groups. Cocaine-exposed boys exhibited lower IQ scores than children in each of the other three groups at age 4, in part due to their lower scores on the Short-term Memory subscale. Exposed boys continued to exhibit lower Short-term memory scores than unexposed boys at 6 years. At 9 years, cocaine-exposed boys still had the lowest IQ scores, but the difference was not significant. In subsequent analyses, early risk factors, maternal verbal IQ, child gender, and other prenatal substance exposures (alcohol, cigarette, and marijuana) are covaried to control for their potential effects on IQ.

Table 2 presents correlations between predictors and children's IQ scores. Living in a stimulating home environment and having a mother with a higher verbal IQ predicted higher IQ scores for both boys and girls. Cocaine exposure predicted lower IQ scores for boys, but not for girls, at ages 4 and 6 years. Neonatal medical problems also predicted lower IQ scores for both boys and girls at 4 years, but not at later years. The maternal stress factor, maternal age-related factor, alcohol exposure, cigarette exposure, and marijuana exposure were unrelated to child IQ. Effects of cocaine exposure on cognitive ability over time, controlling for other variables

Composite IQ scores

To examine whether cocaine effects were present after controlling for other variables and whether the relation between cocaine exposure and child IQ changed over time, a mixed models analysis was conducted (see Table 3). Random effects were specified for the intercept and for the child age coefficient. Cocaine exposure (exposed vs. unexposed)¹ was entered into the model along with environmental risk, gender, neonatal medical risk, and prenatal exposure to alcohol, cigarettes, and marijuana. Interactions between gender and each substance exposure (i.e., cocaine, alcohol, cigarettes, and marijuana) were examined to test whether exposure

¹Analyses using a 3 level cocaine exposure variable (high exposure vs. low exposure vs. no exposure) did not enhance the prediction of children's IQ scores over that of the dichotomous variable (exposure vs. no exposure), so the dichotomous variable was retained in all subsequent analyses.

effects on IQ were greater for boys than girls. Child age was entered to examine whether IQ scores varied by age (contrasting 4- and 6-year IQs, and 4- and 9-year IQs) and to examine whether cocaine exposure interacted with age (i.e., did the effects of cocaine exposure improve or worsen with time?) or with age and gender. However, the interaction of child age and gender was non-significant ($p > .15$) and was removed from the final model. The interactions between gender and prenatal alcohol, cigarette, and marijuana exposure were also included in the initial model but were non-significant and were similarly removed from the final model.

Table 3 and Figure 1 show the effect of cocaine exposure and gender over the 4 to 9 year period. As can be seen in the figure², exposed boys had lower IQs than their unexposed peers, whereas exposure was unrelated to IQ scores for girls (i.e., the cocaine exposure by gender interaction was significant; $t(1367) = 2.37, p < .05$; effect size $d = 0.53$). Main effects were found for the environment as children from a more stimulating environment had higher IQs ($t(572) = 3.48, p < .001; d = 0.65$); maternal verbal intelligence such that high maternal verbal intelligence was related to higher IQs ($t(114) = 3.57, p < .001; d = 0.54$); and time as IQs tended to increase from 4 to 9 years ($t(413) = 6.10, p < .001; d = 0.99$). Main effects for cocaine exposure, other prenatal exposures, neonatal medical risk, and gender were not significant. The interaction between cocaine exposure and child age at both 6- and 9-years (relative to age 4-years) also was not significant, indicating that the negative effects of cocaine exposure on boys' IQs did not significantly vary from 4 to 9 years after controlling for other variables.

Subscale scores

We next examined each of the four Stanford-Binet subscales to identify whether cocaine effects were found for specific subscales (see Table 3). Cocaine and gender interacted such that exposed boys had poorer Abstract/Visual Reasoning scores ($t(594) = 2.06, p < .05; d = 0.47$), with trends for poorer Short-term Memory ($t(2392) = 1.81, p < .10; d = 0.40$) and Verbal Reasoning ($t(1323) = 1.71, p < .10; d = 0.38$) scores. In addition, children from less stimulating environments had poorer Quantitative Reasoning ($t(200) = 2.00, p < .05; d = 0.46$), Short-term Memory ($t(466) = 2.40, p < .05; d = 0.56$), and Verbal Reasoning ($t(592) = 3.03, p < .01; d = 0.68$) scores. Maternal verbal IQ also predicted each subscale, as higher maternal verbal IQ predicted higher child Abstract/Visual Reasoning ($t(119) = 2.73, p < .01; d = 0.41$), Quantitative Reasoning ($t(131) = 2.04, p < .05; d = 0.26$), Short-term Memory ($t(334) = 2.89, p < .01; d = 0.36$), and Verbal Reasoning ($t(252) = 3.76, p < .001; d = 0.52$). In addition, an unexpected relation was found such that prenatal exposure to alcohol predicted higher Quantitative Reasoning scores ($t(643) = 2.24, p < .05; d = 0.32$). The maternal stress factor, maternal age-related factor, prenatal exposure to cigarettes and marijuana, and gender did not predict any subscale. Cocaine exposure was found to interact with child-age in predicting Abstract/Visual Reasoning such that exposed subjects had somewhat lower scores on this subtest at 4 years, but not at 6 years ($t(643) = 2.24, p < .05; d = 0.68$); however, the other 7 cocaine exposure by child-age interactions were not significant, indicating that the negative effects of cocaine exposure on boys' IQs generally did not vary from 4 to 9 years. Main effects, however, were found for child-age on each subscale, as scores increased from age 4- to 9-years.

Discussion

From age 4 to 9 years, prenatal cocaine exposure was related to lower composite IQ scores for boys, but not for girls. The gender specific effect of cocaine exposure was found controlling for prenatal exposure to alcohol, cigarettes, and marijuana, neonatal medical risk, environmental risk, and maternal verbal intelligence. As expected, maternal verbal intelligence and a stimulating home environment at age 4 were also associated with higher child IQ scores. The findings are consistent with prior research indicating that prenatal cocaine exposure may increase developmental risk, especially for boys.

Boys, but not girls, prenatally exposed to cocaine have previously shown deficits in cognitive function, inhibitory control, health risk behaviors, and emotional modulation in the present sample (Bendersky et al., 2003, 2005, 2006; Bennett et al., 2002, 2007; Dennis-Tiway et al., 2006). Cocaine-exposed boys, but not girls, also have exhibited increased central processing, abstraction, arithmetic skills, motor skill, passivity, and externalizing problems in other studies (Bailey et al., 2005; Delaney-Black et al., 2004; Singer et al., 2004). These findings converge with those from animal studies finding exposed male, but not female, rats to perform worse on cognitive, attention, and motor development assessments (Garavan et al., 2000; Gendle et al., 2004; Markowski, Cox, & Weiss, 1998), perhaps due to underlying differences in central noradrenergic or dopaminergic function (Garavan et al.; Glatt, Trksak, Cohen, Simeone, & Jackson, 2004).

Several other possible explanations for the mechanisms by which gender may moderate the relation between cocaine exposure and cognitive outcomes exist. Given that cocaine is associated with greater cerebral vasoconstriction among men than women (Kaufman et al., 2001), it is possible that cocaine also causes greater vasoconstriction among male than female fetuses, producing greater cognitive impairment among males. It also is possible that gender differences found in cognitive ability among cocaine exposed children result from gender differences in oxidative stress. Research has found prenatal cocaine exposure to be associated with both increased oxidative stress in the hippocampus and with memory impairment in rats (Bashkatova, Meunier, Maurice, & Vanin, 2005). Recent research also has found, at least in rats, that males are less able to defend against oxidative damage in brain tissue (Katalinic, Modun, Music, & Boban, 2005). Collectively, these findings suggest that males may incur greater oxidative stress and cognitive impairment secondary to cocaine exposure. Iron deficient anemia (IDA) also might be implicated, as boys are at greater risk for IDA in early childhood (Domellof et al., 2002). IDA has been found to be more prevalent among cocaine-exposed children and to be related to lower IQ scores (Nelson, Lerner, Needlman, Salvator, & Singer, 2004). While the exact mechanism for potential cognitive effects of cocaine exposure remains unknown, there is growing evidence that boys may be more negatively affected. Functional magnetic resonance imaging (fMRI) studies could be helpful in identifying the regions of the brain that are most affected for boys. Likewise, fMRI studies could help to identify whether exposed girls somehow compensate, using their brain differently than unexposed girls to produce the same level of cognitive performance following prenatal cocaine exposure.

Cocaine exposure generally did not interact with child age in predicting IQ, indicating that exposure-related effects persisted into preadolescence. More positively, however, cocaine's relation to IQ did not increase over time. Thus, we did not find evidence of a sleeper effect in which cognitive deficits early on (e.g., at age 4) increase at later ages. Whether IQ deficits found for boys in the present sample will persist, diminish, or increase during adolescence and early adulthood, periods during which cognitive abilities are still maturing (Luna et al., 2004) remains to be seen. Studies with rats suggest that gender differences in exposure effects are greater in adolescence and adulthood (Spear et al., 2002), raising the possibility that exposure related deficits among males may not diminish.

Examination of specific cognitive domains reveals an exposure by gender interaction on abstract/visual reasoning, with trends on short-term memory and verbal reasoning abilities. Although prior reports have not found cocaine effects on the Abstract/Visual Reasoning subscale of the Stanford-Binet from age 3- to 6-years (Bennett et al., 2002; Kilbride, Castor, Hoffman, & Fuger, 2000; Richardson et al., 1996), cocaine exposed children have been found to exhibit deficits on other tasks that involve visual information processing (Heffelfinger, Craft, & Shyken, 1997; Mayes et al., 2007; Singer et al., 1999). Similarly, deficits have been observed in cocaine exposed children's verbal skills and memory, though not consistently (e.g., Frank et al., 2001). Exposed children have shown deficits in verbal reasoning on the Stanford-Binet

(Griffith et al., 1994) and on the verbal factor of another intelligence test (Heffelfinger, Craft, White, & Shyken, 2002), though the relation became non-significant after controlling for maternal verbal ability and environmental risk in one study (Arendt et al., 2004). Young cocaine exposed children have also been found to have delays in expressive language skills (Delaney-Black et al., 2000; Morrow et al., 2004). Given that expressive language is highly related to the verbal reasoning subscale of the Stanford-Binet (e.g., Molfest & Acheson, 1997), such verbal reasoning deficits among cocaine exposed children in the present sample may be the result of poor expressive language skills. Cocaine exposed children have also shown deficits on tasks requiring short-term memory (Jacobson et al., 1996; Mayes, Snyder, Langlois, & Hunter, 2007), consistent with studies finding cocaine exposed rodents to exhibit short-term memory deficits, possibly related to increased oxidative stress in the hippocampus (Bashkatova et al., 2005; Morrow, Elsworth, & Roth, 2002). The lack of an effect, however, on quantitative reasoning contrasts our own 4-year report (Bennett et al., 2002) and that of Singer et al., but it should be noted that the exposure by gender interaction approached a trend ($p = .14$) on the Quantitative Reasoning subscale in the present study.

The present study has several strengths in examining the effects of cocaine exposure through preadolescence. Biological assays were used to verify cocaine exposure status, numerous potential confounding variables were controlled, and the potential moderating effects of gender and child age on IQ were examined. Nonetheless, there are other environmental factors that may have affected children's IQ and that were not controlled, such as involvement in preschool programs (Frank et al., 2005). Likewise, our assessment of mothers' cognitive ability was limited to verbal IQ, and a more comprehensive assessment may have better predicted children's IQs. Finally, these findings are based on an urban, predominantly African American, sample in the United States and may not necessarily generalize to other samples.

The results of the present study suggest that the negative effects of prenatal cocaine exposure on cognitive ability do not dissipate by preadolescence. Though children's environments have now repeatedly been found to exert an effect on exposed children's developmental outcomes, the continued cognitive deficits found for exposed boys controlling for environmental factors in the present sample is concerning. Even modest effects on IQ may have a substantial societal impact (Lester, Lagasse, & Seifer, 1998). The present findings highlight the need to examine gender as a potential moderator of cocaine exposure effects, and to examine the cognitive development of children prenatally exposed to cocaine during the adolescent years.

Acknowledgements

This study was supported by Grant DA07109 to Michael Lewis from the National Institute on Drug Abuse. The authors appreciate the statistical assistance of Charles Cleland.

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Figure 1.
IQ scores as a function of prenatal cocaine exposure and gender (predicted means from the linear mixed model).

Table 1

Means (and standard deviations) of predictor and cognitive functioning variables by cocaine exposure and gender

	Boys (n = 43)	Cocaine exposed Girls (n = 48)	Boys (n = 77)	Unexposed Girls (n = 63)	F (3,146-221)	Total Sample (n = 231)
Predictor variables						
Early risk						
Neonatal Medical Risk factor (Z score)	0.92 ^a (2.23)	0.62 ^a (1.91)	-0.46 ^b (1.38)	-0.53 ^b (0.97)	10.79 ^{***}	0.01 (1.71)
Neonatal medical problems	1.38 ^{ab} (2.32)	1.48 ^a (2.64)	0.71 ^{ab} (1.47)	0.50 ^b (1.21)	3.48 [*]	0.94 (1.91)
Gestational age (weeks)	38.65 ^{ac} (2.75)	38.02 ^a (3.05)	40.25 ^{bd} (1.66)	39.82 ^{cd} (1.96)	10.27 ^{***}	39.36 (2.46)
Stimulating Environment factor (Z score)	-0.08 (0.66)	-0.09 (0.67)	0.14 (0.56)	0.00 (0.53)	2.00	0.01 (0.60)
Academic stimulation (HOME)	4.64 (0.55)	4.62 (0.55)	4.86 (0.43)	4.81 (0.52)	2.63 [#]	4.76 (0.51)
Learning stimulation (HOME)	7.35 (1.98)	7.41 (1.94)	7.28 (2.12)	7.65 (1.73)	0.37	7.42 (1.95)
Language stimulation (HOME)	5.76 (1.25)	6.00 (1.30)	6.17 (0.91)	5.81 (1.18)	1.40	5.96 (1.14)
Encouragement of maturity (HOME)	2.52 (1.23)	2.30 (1.05)	2.50 (1.27)	2.47 (1.22)	0.24	2.46 (1.20)
Variety in experience (HOME)	7.36 (1.37)	7.18 (1.36)	7.38 (1.37)	7.31 (1.10)	0.21	7.32 (1.28)
Warmth and acceptance (HOME)	5.11 (1.71)	4.83 (1.49)	5.29 (1.16)	4.96 (1.53)	0.93	5.08 (1.44)
Maternal education (years)	11.82 (1.16)	11.55 (1.41)	11.63 (1.21)	11.11 (1.62)	2.13 [#]	11.49 (1.39)
# of caregivers in home	1.55 (0.46)	1.64 (0.41)	1.76 (0.40)	1.65 (0.36)	2.36 [#]	1.67 (0.41)
Maternal Stress factor (Z score)	0.27 ^a (0.66)	0.39 ^a (0.74)	-0.22 ^b (0.59)	-0.20 ^b (0.69)	12.62 ^{***}	0.00 (0.72)
Negative life events (SEI)	7.09 (4.84)	7.46 (4.43)	7.08 (4.24)	6.82 (4.11)	0.18	7.08 (4.33)
Depressive symptoms (BDI)	7.16 (5.02)	7.26 (7.06)	6.26 (6.04)	6.02 (5.11)	0.62	6.57 (7.06)
Instability of child's surroundings (FCS)	0.33 (0.48)	0.21 (0.41)	0.32 (0.47)	0.33 (0.47)	0.68	0.30 (0.46)
Kinship or foster care (# of placements)	0.23 ^{abc} (0.43)	0.41 ^b (0.50)	0.05 ^{cd} (0.23)	0.00 ^{de} (0.00)	14.04 ^{***}	0.15 (0.36)
Public assistance (TANF)	0.39 (0.47)	0.44 (0.45)	0.26 (0.41)	0.34 (0.40)	1.78	0.34 (0.43)
Maternal Age-related factor (Z score)	0.39 ^a (0.68)	0.36 ^a (0.65)	-0.21 ^b (0.70)	-0.27 ^b (0.65)	15.28 ^{***}	0.00 (0.74)
Maternal age at child's birth	29.27 ^a (4.99)	28.30 ^a (3.93)	24.23 ^b (5.91)	23.68 ^b (6.32)	13.30 ^{***}	25.82 (5.99)
# prior births	2.43 ^a (1.95)	2.63 ^a (1.84)	1.37 ^b (1.74)	1.37 ^b (1.19)	8.43 ^{***}	1.81 (1.75)
Child's father in household	0.55 (0.46)	0.55 (0.48)	0.37 (0.44)	0.35 (0.42)	3.07 [*]	0.43 (0.45)
Maternal verbal IQ	71.74 (13.40)	71.24 (11.34)	72.58 (15.82)	75.09 (15.43)	0.57	72.80 (14.34)
Prenatal substance exposure						
Alcohol (drinks/day)	0.91 ^{ab} (1.54)	1.85 ^a (3.74)	0.03 ^b (0.14)	0.01 ^b (0.06)	12.37 ^{***}	0.53 (1.90)
Cigarettes (per day)	7.78 ^a (7.63)	11.62 ^b (11.74)	1.22 ^c (4.42)	1.17 ^c (3.29)	29.38 ^{***}	4.40 (8.05)
Cocaine (grams/day)	0.46 ^a (0.64)	0.68 ^a (0.93)	0.00 ^b (0.00)	0.00 ^b (0.00)	23.99 ^{***}	0.19 (0.55)
Marijuana (joints/day)	0.07 ^{ab} (0.19)	0.49 ^a (1.86)	0.03 ^b (0.23)	0.05 ^b (0.03)	3.59 [*]	0.12 (0.84)
Child IQ (composite score)						
4 year IQ						
Abstract/visual reasoning	78.13 ^a (10.23)	86.72 ^b (11.81)	85.08 ^b (11.81)	86.16 ^b (11.97)	4.83 ^{**}	84.50 (11.91)
Quantitative reasoning	80.63 ^a (12.34)	87.88 ^{ab} (11.67)	86.39 ^{ab} (13.01)	88.10 ^b (11.90)	3.36 [*]	86.17 (12.52)
Short-term memory	86.33 (10.60)	92.47 (13.76)	90.03 (11.16)	90.31 (12.92)	1.44	90.02 (12.25)
Verbal reasoning	81.79 ^a (11.14)	88.72 ^b (9.48)	89.96 ^b (11.76)	92.39 ^b (10.80)	7.66 ^{***}	88.97 (11.45)
6 year IQ						
Abstract/visual reasoning	81.61 (11.10)	87.77 (15.42)	85.80 (13.30)	84.14 (16.56)	1.38	84.98 (14.45)
Quantitative reasoning	84.24 (13.44)	91.45 (10.99)	90.74 (14.12)	88.82 (13.02)	2.31 [#]	89.24 (13.19)
Short-term memory	87.28 (16.59)	94.71 (14.64)	92.10 (16.63)	87.88 (18.51)	1.86	90.73 (16.84)
Verbal reasoning	83.39 (17.21)	89.51 (16.47)	88.49 (16.00)	88.33 (20.81)	0.84	87.76 (17.69)
9 year IQ						
Abstract/visual reasoning	87.73 ^a (10.17)	94.36 ^{ab} (9.76)	96.05 ^b (13.27)	94.41 ^{ab} (11.83)	3.84 ^{**}	93.75 (11.90)
Quantitative reasoning	89.09 (11.18)	92.19 (10.04)	93.97 (16.80)	91.98 (11.02)	1.00	92.17 (13.07)
Short-term memory	89.96 (10.63)	92.63 (10.25)	93.87 (11.29)	92.02 (12.19)	0.69	92.36 (11.19)
Verbal reasoning	93.62 (12.34)	98.69 (10.49)	97.47 (13.30)	95.09 (13.21)	1.09	96.39 (12.52)
Abstract/visual reasoning	92.31 (12.08)	90.86 (15.15)	91.64 (11.93)	90.73 (13.18)	0.10	91.31 (13.02)
Short-term memory	89.65 (01.57)	94.74 (10.07)	95.58 (12.47)	96.68 (13.13)	2.07	94.68 (11.97)
Verbal reasoning	90.88 (12.72)	90.89 (13.24)	94.64 (14.04)	90.86 (13.06)	0.84	92.01 (13.33)

Note. BDI = Beck Depression Inventory; FCS = Family Chaos Scale; HOME = Home Observation for Measurement of the Environment; SEI = Social Environment Inventory; TANF = Temporary Assistance for Needy Families.

Note. Neonatal medical problems, alcohol exposure, cigarette exposure, and marijuana exposure variables were each log transformed to correct for skew in all subsequent analyses.

Note. Means with different superscripts indicate significant between group differences at $p < .05$.

$p \leq .10$.
 * $p \leq .05$.
 ** $p \leq .01$.
 *** $p \leq .001$.

Table 2
Pearson correlations among predictor and cognitive functioning variables (below diagonal = boys; above diagonal = girls)

	1. Neo Med	2. Stim Env	3. Mat Stress	4. Mat Age	5. Mat VIQ	6. Alc	7. Cig	8. Coc	9. Marij	10. IQ (4 yrs)	11. IQ (6 yrs)	12. IQ (9 yrs)
Predictor variables												
1. Neonatal Medical risk factor	--	-.10	-.03	.25**	-.10	.25**	.30**	.38***	.15	-.26**	-.17	-.09
2. Stimulating Environment factor	-.21*	--	-.32***	-.17#	.43***	-.01	-.08	-.07	.07	.35***	.28***	.29***
3. Maternal Stress factor	.01	-.37***	--	.03	-.15	-.39***	.01	.20*	.02	-.18#	-.18#	-.14
4. Maternal Age- related factor	.17#	-.26**	.07	--	-.06	.35***	.38***	.44***	.03	-.11	-.09	-.12
5. Maternal verbal IQ	-.13	.35***	-.07	.02	--	-.03	-.05	-.13	.07	.38***	.35***	.35***
6. Prenatal alcohol exposure	.24**	-.15#	-.09	.16#	-.12	--	.45***	.65***	.25**	.09	.13	.07
7. Prenatal cigarette exposure	.20*	-.20*	-.01	.36***	-.16#	.52***	--	.66***	.34***	.01	.11	.04
8. Prenatal cocaine exposure	.38***	-.18#	-.07	.38***	-.09	.58***	.68***	--	.32***	.00	.12	.04
9. Prenatal marijuana exposure	.03	-.03	-.03	-.09	.07	.38***	.31***	.32***	--	.01	-.02	-.09
Child IQ (composite score)												
10. IQ - 4 years	-.26**	.45***	-.08	-.06	.37***	-.12	-.13	-.26**	-.12	--	.67***	.61***
11. IQ - 6 years	-.16#	.31***	-.13	-.07	.24**	-.04	-.18	-.21*	-.15	.68***	--	.76***
12. IQ - 9 years	-.11	.24**	.01	-.07	.25**	-.01	-.11	-.14	-.12	.59***	.78***	--

Note. Cocaine exposure was entered as a dichotomous variable (0 = no exposure; 1 = exposed).

#

$p \leq .10$.

*

$p \leq .05$.

**

$p \leq .01$.

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$p \leq .001$.

Table 3
Coefficients (and standard error; followed by 95% confidence intervals) from mixed model analyses predicting Stanford-Binet IV IQ and subscales

	IQ Composite	Abstract/Visual Reasoning	Quantitative Reasoning	Short-term Memory	Verbal Reasoning
Predictors					
Neonatal Medical risk factor	-0.21 (0.93; -2.03 to 1.61)	0.40 (1.05; -1.67 to 2.47)	-0.64 (1.02; -2.63 to 1.36)	-0.52 (0.87; -2.22 to 1.18)	-0.06 (0.98; -1.99 to 1.86)
Stimulating Environment factor	3.79 (1.45; 0.93 to 6.64) ^{**}	1.92 (1.68; -1.39 to 5.22)	3.46 (1.73; 0.05 to 6.87) [*]	3.27 (1.36; 0.59 to 5.92) [*]	4.45 (1.47; 1.57 to 7.32) ^{**}
Maternal Stress factor	-1.14 (1.54; -4.15 to 1.88)	-1.70 (1.70; -5.04 to 1.64)	-2.35 (1.79; -5.87 to 1.17)	0.15 (1.49; -2.78 to 3.08)	-0.24 (1.62; -3.42 to 2.93)
Maternal Age-related factor	-0.81 (1.14; -3.06 to 1.44)	0.11 (1.23; -2.29 to 2.52)	0.87 (1.31; -1.72 to 3.45)	-1.52 (1.09; -3.66 to 0.61)	-1.31 (1.19; -3.64 to 1.03)
Maternal verbal IQ	3.16 (0.91; 1.35 to 4.96) ^{***}	2.79 (1.02; 0.77 to 4.80) ^{**}	2.04 (1.00; 0.06 to 4.01) [*]	2.20 (0.76; 0.70 to 3.69) ^{**}	3.21 (0.85; 1.53 to 4.88) ^{***}
Prenatal alcohol exposure	1.41 (0.94; -0.44 to 3.27)	0.67 (1.09; -1.48 to 2.82)	2.34 (1.04; 0.29 to 4.40) [*]	0.65 (0.90; -1.12 to 2.42)	1.13 (1.01; -0.86 to 3.13)
Prenatal cigarette exposure	0.64 (0.97; -1.26 to 2.54)	-0.50 (1.11; -2.68 to 1.69)	0.28 (1.10; -1.87 to 2.43)	1.25 (0.95; -0.62 to 3.12)	0.30 (1.01; -1.69 to 2.28)
Prenatal cocaine exposure	0.45 (2.79; -5.03 to 5.92)	1.93 (3.26; -4.46 to 8.33)	1.42 (3.44; -5.32 to 8.17)	-2.71 (2.72; -8.04 to 2.63)	3.42 (2.93; -2.32 to 9.16)
Prenatal marijuana exposure	-1.29 (0.80; -2.87 to 0.29)	-0.57 (0.91; -2.36 to 1.22)	-1.13 (0.90; -2.90 to 0.64)	-0.78 (0.79; -2.34 to 0.78)	-0.98 (0.83; -2.60 to 0.64)
Child gender (0=girls, 1=boys)	0.07 (1.88; -3.62 to 3.76)	0.52 (2.06; -3.53 to 4.56)	-0.37 (1.98; -4.26 to 3.52)	-1.89 (1.69; -5.19 to 1.42)	1.26 (1.89; -2.45 to 4.97)
Age: 4- vs. 6-years	3.42 (0.92; 1.61 to 5.23) ^{***}	1.77 (1.44; -1.05 to 4.59)	2.29 (1.73; -1.12 to 5.69)	4.40 (1.17; 2.10 to 6.69) ^{***}	6.56 (1.08; 4.43 to 8.68) ^{***}
Age: 4- vs. 9-years	6.20 (0.98; 4.27 to 8.12) ^{***}	8.32 (1.46; 5.44 to 11.19) ^{***}	5.13 (1.69; 1.82 to 8.45) ^{**}	3.88 (1.23; 1.47 to 6.30) ^{**}	7.11 (1.21; 4.72 to 9.49) ^{***}
Prenatal cocaine exposure X gender	-6.47 (2.83; -12.02 to -0.93) [*]	-6.80 (3.29; -13.26 to -0.33) [*]	-4.67 (3.16; -10.88 to 1.54)	-4.75 (2.62; -9.89 to 0.39) [#]	-4.98 (2.92; -10.72 to 0.75) [#]
Age 4- vs. 6-years X cocaine exposure	1.26 (1.45; -1.59 to 4.11)	4.52 (2.26; 0.08 to 8.96) [*]	-2.21 (2.88; -7.87 to 3.46)	1.31 (1.83; -2.28 to 4.91)	1.43 (1.75; -4.87 to 2.01)
Age 4- vs. 9-years X cocaine exposure	1.33 (1.53; -1.69 to 4.34)	2.39 (2.27; -2.07 to 6.86)	-0.19 (2.81; -5.72 to 5.34)	1.88 (1.98; -2.02 to 5.79)	-0.79 (1.74; -4.21 to 2.63)

Note. Cocaine exposure was entered as a dichotomous variable (0 = no exposure; 1 = exposed). Age was coded such that 4-years is the referent to which the other ages are compared.

[#] $p \leq .10$.

^{*} $p \leq .05$.

^{**} $p \leq .01$.

^{***} $p \leq .001$. (2-tailed).