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Influence of Prenatal Cocaine Exposure on Early Language Development: Longitudinal Findings from Four Months to Three Years of Age

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Abstract

The influence of prenatal cocaine exposure on children's language functioning was evaluated longitudinally at six time points from 4 months to 3 years of age. The Miami Prenatal Cocaine Study prospectively enrolled 476 full-term African-American infants at birth, categorized as cocaine-exposed (n = 253) or non-cocaine-exposed (n = 223) by maternal self-report and bioassays (maternal/infant urine, meconium). The Bayley Scales of Infant Development, scored using the Kent Scoring Adaptation for language, was administered at 4, 8, 12, 18, and 24 months. The Clinical Evaluation of Language Fundamentals-Preschool was administered at 3 years. In longitudinal analyses using Generalized Estimating Equations, cocaine-exposed children had lower overall language skills than non-cocaine-exposed children (D = -0.151; 95% CI = -0.269, -0.033; p = .012). Longitudinal findings remained stable after evaluation of potential confounding influences including other prenatal substance exposures and sociodemographic factors. Preliminary evidence also indicated possible mediation through an intermediary effect involving cocaine-associated deficits in fetal growth.

Determining the relative influence of prenatal cocaine exposure on long-term child development has remained a complicated and often controversial issue, in part because of the complex interplay of numerous biological and environmental factors that must be considered when evaluating prenatal cocaine exposure's impact on the developing child. Cocaine's potential for exerting a teratogenic influence on both structural and functional aspects of fetal brain development have been well documented, particularly within animal models,[1-4] with mechanisms of influence primarily hypothesized by alterations in developing monoaminergic neurotransmitter systems.[2,5] Indirect pathways have also been hypothesized because of the vasoconstrictive effects of cocaine on maternal blood flow, which impair placental blood flow and may lead to maternal hyper-tension, fetal vasoconstriction, and episodes of fetal hypoxia.[2,4,6-8]

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Given the complexities of fetal development and its potential to interact with the timing and dosage of prenatal cocaine exposure, the hypothesized effects of cocaine exposure have typically encompassed a broad spectrum of prenatal and postnatal developmental processes. Cocaine-related effects have been documented during the prenatal period, including decrements in fetal growth,[9-18] reduced gestational age,[15,16] spontaneous abortion,[15] and maternal and infant death.[19-22] Subtle cocaine-related alterations in functional brain maturation during the first year of life have also been observed.[23] A decade of research focused primarily on the infancy and toddler period suggests that prenatal cocaine exposure, although not as clinically devastating as first indicated by early research, may lead to subtle neurobehavioral impairments, increasing long-term risk for learning and social/behavioral difficulties.[24-28] Language functioning during early childhood is of particular concern because of the possibility that early language deficits may impair long-term social adaptation and academic success.[29,30]

Existing studies, although often limited by methodological constraints, have documented an emerging pattern suggestive of language deficits in cocaine-exposed children. Several studies, using standardized assessment measures, have noted significant differences in receptive or expressive language abilities when comparing cocaine-exposed children with non-cocaine-exposed children.[31-38] In a more recent well-controlled prospective study, Singer and colleagues[39] reported poorer auditory comprehension scores in more heavily exposed infants than nonexposed infants and lower total language scores than both less-exposed and nonexposed infants at 1 year of age. Several other studies, however, including a larger prospective study performed by Hurt and colleagues[40] have not documented differences in language abilities on standardized assessments.[40-43]

Studies using spontaneous language samples to evaluate semantic and syntactical processing elements of language have found evidence of phonological delay,[44] differences in discourse pragmatics, and, to a lesser extent, syntactic development[45] when comparing cocaine-exposed with non-cocaine-exposed toddlers and preschool children. Similarly, Malakoff and colleagues[46] found that cocaine-exposed 2-year-old children exhibited less complex language skills when compared with non-cocaine-exposed children, as measured by shorter mean utterances and less complex grammatical structure and language production. Bland-Stewart and colleagues[47] found more delayed and restricted semantic representations in 2-year-old children exposed prenatally to cocaine but did not find differences in sequences of semantic development, utterance length or type, or overall receptive and expressive language development. Reporting the largest well-controlled study to date (n = 458), Delaney-Black and colleagues[48] also found no mean differences on a proficiency scale or on several expressive language variables derived from the language samples of 6-year-old children. These researchers did find cocaine-exposure status could be predicted by combining cutoffs for two language sample variables, indicating a threshold effect for cocaine-related language deficits.

Although previous studies suggest an emerging pattern of cocaine-related language effects, methodological limitations including small sample sizes, nonprospective study designs, and failure to statistically control for other prenatal substance exposures or confounding influences make it difficult to ascertain a cocaine-specific effect on language development. The current report, derived from the Miami Prenatal Cocaine Study (PCS), investigates the influence of prenatal cocaine exposure on children's language functioning measured over six time points from 4 months to 3 years of age. The Miami PCS is a longitudinal investigation of the effects of prenatal cocaine exposure on long-term child development. Study participants were enrolled prospectively at birth with verification of substance exposure status using biological markers and maternal self-report. The current report uses longitudinal multivariate statistical methods to evaluate potentially confounding factors, including other prenatal drug exposures, infant birth parameters, maternal/caregiver demographics, and important postnatal social

environmental factors. Given the documented relationship between prenatal cocaine exposure and decreased fetal growth,[9-18] and to a lesser extent decreased gestational age,[15,16] these factors were investigated as hypothesized mediators of the relationship between prenatal cocaine exposure and language functioning.

METHODS

Study Participants

The Miami Prenatal Cocaine Study (PCS) follow-up sample consisted of 253 cocaine-exposed (with or without concomitant use of alcohol, tobacco, or marijuana) and 223 cocaine-free comparison infants (76 were exposed to varying combinations of alcohol, tobacco, or marijuana during pregnancy and 147 were drug-free). The study sample was homogeneous with regard to full-term gestational age, low socioeconomic status, inner-city residence, and African-American race/ethnicity. Enrollment exclusion criteria included maternal HIV/AIDS; prenatal exposure to opiates, methadone, amphetamines, barbiturates, benzodiazepines, or phencyclidine; major congenital malformation; chromosomal aberration; and disseminated congenital infection. The current report focuses on the hypothesized impact of prenatal cocaine exposure on language development measured at 4, 8, 12, 18, and 24 months, and 3 years. Among the sample's 476 full-term African-American children, 464 received at least one language assessment during the study period and were included in the present report.

Study Design and Recruitment

The overall study design and recruitment of the follow-up cohort for the longitudinal Miami PCS has been detailed in a separate report.[9] The study was approved by the institutional review board and performed under a federal Department of Health and Human Services Certificate of Confidentiality. The original study involved an epidemio-logical survey of 1505 mothers interviewed at birth and longitudinal follow-up of 476 mother-infant dyads enrolled from the survey cohort. African-American mothers born in the United States and residing in designated geographical areas were recruited from the delivery service of the University of Miami School of Medicine Jackson Memorial Medical Center between November 1990 and July 1993. Study enrollment was restricted to one full-term infant from each mother. Labor and delivery admission records identified 2651 full-term live births to African-American mothers born in the United States and residing in the designated geographical area. Of these, 171 infants from twin and multiple births were excluded after random selection of one twin's data for inclusion. An additional 383 mothers were not approached for consent because of scheduling and staffing constraints, maternal cognitive and psychological limitations, early maternal discharge, inaccessibility of the mother for other reasons, and conflict with other research protocols. Of the 2097 (85%) approached for consent, 1505 (72%) agreed to study participation. Hospital records indicated that mothers who participated in the survey were somewhat younger than those who did not (mean ± SD: 23.6 ± 5.7 vs. 24.9 ± 5.9, $p < .05$). They also were more likely to be primigravida (25.4% vs. 19.5%, $p < .001$) and to have received prenatal care (93.9% vs. 91%, $p < .001$). Participating infants were more likely to have lower Apgar scores ≤8 in contrast with nonparticipating infants (19.7% vs. 15.8%, $p < .05$).

Of the 1505 mothers participating in the survey, 154 were determined ineligible for the follow-up study because of positive or unknown maternal HIV status, and 25 additional cases were excluded for exposure to heroin or other drugs (not including alcohol, tobacco, and marijuana). From the remaining 1326 eligible full-term infants, an attempt was made to engage all identified cocaine-exposed infants into the follow-up study. A secondary goal was to enroll cocaine-free infants with exposure to alcohol. Of these, 89% of cocaine-exposed infants and 80% of cocaine-free infants exposed to alcohol, tobacco, and/or marijuana (with a minimum ingestion criterion of 20 drinks of alcohol during pregnancy) were enrolled. Drug-free infants (negative self-report

for all drugs during pregnancy and the 3 months preceding pregnancy and negative results on all available toxicology assays) were enrolled from the remaining pool of eligible infants using a random numbers table to balance the number of drug-free comparison infants recruited across the study period.

Substance Exposure Classification—Prenatal cocaine exposure was determined by maternal self-report of cocaine use during pregnancy or by at least one gas chromatography/mass spectrometry-confirmed cocaine-positive biological marker, including maternal urine, infant urine, and meconium. Alcohol and tobacco exposure were determined by self-report, and marijuana exposure was indicated by self-report or a positive toxicology screen. Of the 253 cocaine-exposed infants in the follow-up cohort, 40 cases (16%) were identified as cocaine-exposed solely on the basis of positive maternal self-report. In 80 cases (32%), the mother denied cocaine use during pregnancy, but one or more biological markers were cocaine positive. Cocaine-free infants had mothers with negative self-report histories for cocaine use during and 3 months preceding pregnancy and negative results on all available toxicology assays. Of the non-cocaine-exposed infants, 92% were designated as cocaine-free on the basis of meconium and urine toxicology results. The remaining 8% were categorized on the basis of self-report and urine toxicology results. For the subset of non-cocaine-exposed infants identified as drug-free, mothers also reported no known lifetime cocaine use and no known use of other drugs during pregnancy or the 3 months before conception.

Data Collection Procedures

During the immediate postpartum period, experienced research staff performed a standardized research interview and organized the collection of the biological specimens. Trained research personnel, blinded to exposure status, performed the Ballard gestational age assessment[49] within 36 hours of delivery and obtained occipitofrontal head circumference and recumbent crown-heel birth length. Pertinent maternal and infant medical and demographic information were collected from the medical record at birth. Caregiver and child data relevant to the present study were drawn from serial developmental assessments performed at 4, 8, 12, 18, and 24 months and 3 years of age. Examiners blinded to substance exposure status performed all child assessments.

Prenatal Substance Exposure Measures

Maternal Interview—A structured standardized interview was performed by trained research staff within the first 36 hours postpartum to ascertain maternal substance use and additional demographic information. To enhance timeline recall, targeted recall periods were outlined and anchored to important calendar dates. Drug use questions during pregnancy were asked by trimester and included number of weeks used, most days per week, fewest days per week, usual days per week, and usual dose per day.

Prenatal Substance Exposure Variables—Dosage was measured in the number of cigarettes smoked, number of marijuana joints smoked, number of drinks of beer, wine, or hard liquor, and number of cocaine lines or rocks and was recorded in increments of usual daily dose, usual days per week, and number of weeks used. Standardized definitions[50] were used for determining one-drink units for each type of alcohol (beer 12 oz, wine 5 oz, and liquor 1.5 oz). Pregnancy exposure composites were calculated for each drug by multiplying the number of weeks used by the usual days per week and the usual dose per day. The total pregnancy self-report composites are presented descriptively in Table 1 to reflect the median cohort exposure levels based on self-report data. Pregnancy exposure composites for alcohol, tobacco, and marijuana were used as covariates in all analyses. A dichotomous grouping indicator for cocaine exposure (yes/no) was used to evaluate the influence of prenatal cocaine exposure on language performance over time.

Biological Markers (Meconium and Urine)—Screening of urine and meconium for cocaine metabolite (benzoylecgonine) was performed by EMIT® (Syva DAU, San Jose, CA) at a cutoff of 150 ng/mL urine and 150 ng/gm meconium, respectively, and cocaine-positive specimens were confirmed by gas chromatography/mass spectrometry.[51] Urine specimens were also assayed by EMIT® for marijuana (cannabinoids), opiates, amphetamines, barbiturates, benzodiazepines, and phencyclidine. Meconium specimens were also assayed by EMIT® for marijuana and opiates. Of the total sample, 100% had at least one biological marker, 96% had at least two biological markers, and 68% had all three biological markers available for screening. Infant urine was collected in 98% and maternal urine in 79% of the total follow-up sample, with no differences among the groups in collection rates. A maternal or infant urine screen was performed on all but one of the 476 enrolled infants. Infant meconium was collected on 86% of the total sample with a slightly higher collection rate among non-cocaine-exposed infants (91% vs. 82% for cocaine-exposed infants). In the cocaine-exposed group, of the 18% categorized by urine without meconium, 74% reported positive cocaine use.

Infant/Child Measures

Bayley Scales of Infant Development—Developmental assessments were performed at approximately 4, 8, 12, 18, and 24 months. The original Bayley Scales of Infant Development (BSID)[52] was performed because the data collection period occurred before the release of the current revised version. The original BSID is a standardized developmental assessment with good psychometric validity[53] spanning the 2- to 30-month age range. Standardized scoring of BSID raw score totals yields a separate Mental Developmental Index and Physical Developmental Index, based on an age-normative U.S representative sample of 1262 children. The BSID, however, was originally published in 1969, and normative scores are not likely to be representative of the urban African-American children evaluated during the early 1990s in the current sample. Accordingly, emphasis was placed on evaluation of between-group variation. The Kent Scoring Adaptation[54] of the BSID, which provides an age-equivalent scoring system for BSID Mental Scale items based on those items identified as heavily language dependent, was used to provide a more specific measure of language functioning than reflected in the Mental Development Index. Language items, grouped by face valid content, were scored in comparison to the BSID's item age norms, yielding a Developmental Language Age in months, and age adjusted by dividing by the child's age in months and multiplying by 100.

Clinical Evaluation of Language Fundamentals-Preschool—The Clinical Evaluation of Language Fundamentals-Preschool (CELF-P),[55] performed at the 3-year research visit, is an individually administered test of expressive and receptive language ability for children aged 3 to 6 years. The CELF-P was standardized on 800 preschoolers, representative of the U.S. population with regard to gender, race/ethnicity, parent education level, and geographic region. Internal consistency estimates for the three composite scores ranged from .73 to .96 across age groups, and test-retest coefficients for 2- to 4-week intervals were generally high (i.e., .87 to .97). The CELF-P showed moderate to high correlation with other measures of preschool language functioning (e.g., the Preschool Language Scale-3 and the Wechsler Preschool and Primary Scale of Intelligence-Revised) and discriminated between children with and without diagnosed language disorders.[55] The Total Language Score from the CELF-P was used as the language outcome measure at 3 years of age.

McCarthy Scale of Children's Abilities—The McCarthy Scale of Children's Abilities[56] assesses cognitive and motor development in children aged 2 to 8 years, yielding six subscales and a General Cognitive Index that combines the verbal, perceptual-performance, and quantitative scales. The McCarthy General Cognitive Index summary index, assessed at

3 years, was included in analyses to evaluate the influence of cocaine exposure on language functioning independently of global cognition.

Behavioral Audiometry—Hearing was assessed at 3 years of age using play audiometry techniques for children sufficiently mature to respond appropriately to sound stimulation through earphones. For children who were unable to complete the play audiometry task, visual reinforcement audiometry in the sound field was used to obtain reasonable estimates of hearing sensitivity. All testing and interpretations were performed at the University of Miami Mailman Center for Child Development by a licensed, certified pediatric audiologist. For the purposes of the current longitudinal total language analyses, behavioral audiometry results were coded as normal or abnormal in one or both ears (0-2). Minimum response levels of 30 dB were considered abnormal.

Blood Lead Levels—Capillary blood levels, drawn at the 3-year research visit, were performed at the State of Florida Department of Health Laboratory. Blood lead levels 10 μg/dL or greater were confirmed by repeat specimen obtained by venipuncture.

Postnatal Caregiver Measures

Psychosocial Interview—A structured psychosocial interview covering information from birth to 3 years was performed with the mother or primary caregiver of each child during the 3-year assessment visit. The primary caregiver was defined as any family member or custodial guardian responsible for the physical, emotional, and financial well-being of the child. Biological mothers residing with and parenting the child were always prioritized for interview purposes as the primary caregiver, although occasionally another caregiver residing with the child completed the measures. Pertinent psychosocial variables were drawn from this interview to be used as covariates within the analyses.

Statistical Analyses

Initial procedures were performed to evaluate the distributions of all variables, including visual inspection of frequency distributions and longitudinal plots for individual subjects. The relationship between prenatal cocaine exposure (presence/absence) and the selected language measures was estimated using generalized estimating equations (GEE)[57] within a general linear model (GLM). In the GLM/GEE analyses, the estimated size of the hypothesized cocaine effect on language functioning was of primary interest. In this context, 95% CI and *p* values were used as an aid to interpretation, with alpha set at 0.05. The effect estimates, 95% CIs, and *p* values were estimated using STATA Version 6 (Stata Corp., College Station, TX) and its xtgee procedures. The working correlation structure was exchangeable (compound symmetry), with robust estimation of the SEs, allowing for departures from the associated assumptions. These modeling procedures accommodate the longitudinal interdependency of observations within the error structure of the model and allow for use of all available data at each age point, unlike repeated measures analysis of variance, which limits case inclusion by requiring availability of data at all age points under study.

All of the GLM/GEE models evaluated included a dummy-coded (0/1) dichotomous indicator for prenatal cocaine exposure and a term for the age of the child at each assessment visit. To facilitate interpretation of effect estimates, language scores for each assessment visit (Kent Developmental Language Age at 4, 8, 12, 18, and 24 mo; the CELF-P Total Language Score at age 3 yr) were standardized by converting the sample mean for each assessment visit to zero, with a standard deviation of 1, allowing the scores at each assessment visit to vary similarly along this continuum. For the purpose of clinical interpretation, the actual nontransformed scores are presented in Table 2.

The first model performed with GLM/GEE procedures expressed the language score as a function of prenatal cocaine exposure and included statistical adjustment for the child's age at each language assessment. This initial model provided a starting estimate for the magnitude of the cocaine-associated deficit in language functioning. To evaluate confounding influences, each covariate was entered separately in the baseline regression model, and the size of the cocaine-associated language deficit was compared before and after this statistical adjustment. Covariates were retained in subsequent models as a potential confounder if the cocaine-related estimate in the covariate-adjusted model shifted above or below the 1 SE range of the initial model's cocaine slope estimate. Covariates were also retained in subsequent models if they exhibited a relationship to language function ($p \leq .10$) to allow for inclusion of potential confounding variables that may not meet the first criterion.[58] Mediating influences were evaluated using the methodology outlined by Baron and Kenny.[59] The effect of prenatal cocaine exposure on language functioning was evaluated without the suspected mediator and then with the suspected mediator included in the model. Support for the mediating hypothesis was ascertained if the cocaine-language effect estimate was reduced with statistical adjustment for the suspected mediator.

RESULTS

Sample Demographics

Among the original sample's 476 full-term African-American infants, 464 children received at least one language assessment during the longitudinal study period and were included in the present study analyses. Tables 3 and 4 present a description of sample characteristics measured at birth and the 3-year follow-up visit. Table 1 presents the self-reported rates and median amounts of alcohol, marijuana, tobacco, and cocaine use during pregnancy. Median amounts are reported because of the significant skew in self-report data, with a small group of extremely heavy users in each group influencing mean scores. As Table 1 depicts, cocaine use covered the range from mild and moderate to more severe use. In addition, in the cocaine-exposed group 23% reported cocaine use only, 32% reported crack use only, 14% reported cocaine and crack use in combination, and the remaining 31% did not acknowledge cocaine use.

Table 2 summarizes the mean language scores and examination ages by group at each of the six assessment visits. Of the 464 children included in this report, 50% completed all six language assessments, 23% completed five assessments, 13% completed four assessments, 8% completed three assessments, 4% completed two assessments, and 3% completed only one assessment. A total of 439 children returned for the 3-year assessment visit. Of these, 12 children were not testable using standardized assessments because of severe cognitive or behavioral difficulties, although the groups did not differ in the percentage of untestable children. Three additional children had incomplete examinations. At the 3-year assessment, a greater percentage of children in the cocaine-exposed group had scores below 70, or 2 SDs below the standardized sample mean, than in the non-cocaine-exposed group (cocaine-exposed: 38.9%, non-cocaine-exposed: 27.8%; $p = .015$).

Longitudinal Modeling

Baseline Modeling—An initial model, controlling only for the child's age at each exam, was run to provide a baseline estimate of the influence of prenatal cocaine exposure on language functioning over time without adjustment for other confounding influences. As shown in Table 5, Model 1, the initial longitudinal model provided evidence of a modest cocaine-associated deficit in language performance equivalent to approximately 15% of a SD (estimated difference between cocaine-exposed and non-cocaine-exposed infants, D = -0.151; 95% CI = -0.269, -0.033; $p = .012$). Estimates for each individual assessment visit were derived by fitting a regression model to each visit's data, allowing a separate estimate of cocaine-associated deficit

for each time point. The resulting estimates of the cocaine-associated deficit were as follows: 4 months, D= -0.012, p = .916; 8 months, D = -0.111, p = .310; 12 months, D = -0.047, p = .649; 18 months, D = -0.266, p = .007; 24 months, D = -0.141, p = .145; and 3 years, D = -0.241, p = .012. The summary estimate for the cocaine-associated deficit in language performance (p = .012) served well as a common slope estimate of the cocaine-associated deficit longitudinally and was retained as the base model for subsequent analyses.

Evaluation of Covariates—Selected covariates were evaluated separately within the baseline model. The potential for confounding was investigated using the range of variation established in Model 1 (-0.15 ± 0.06 (SE) = -0.21, -0.09), with covariates being retained for further modeling when inclusion in the base model shifted the cocaine-language estimate beyond the specified range or if the covariate exhibited an individual relationship with language functioning when entered into the baseline model ($p \leq .10$).

Maternal/Infant Characteristics at Birth—Child gender, maternal age, education level (years education), current employment (yes/no), marital status (yes/no), prenatal care visits (≤4 visits, >4 visits), and prenatal exposure to alcohol, marijuana, and tobacco (total pregnancy exposure composites) were each evaluated within the baseline model but did not meet the change in estimate criteria for confounding. Child gender and prenatal exposure to alcohol were related to language functioning and retained for statistical modeling. As depicted in Table 5, Model 2, the estimated cocaine-associated language deficit did not change appreciably when child gender was included (D = -0.150; 95% CI = -0.267, -0.033; p = .012). Evaluation of product terms indicated no appreciable variation in the level of cocaine-associated language deficit for male versus female children; however, overall gender differences in language performance were evident, with boys lagging behind girls in language functioning (D = -0.183; 95% CI = 0.301, -0.065; p = .002).

When terms for alcohol, tobacco, and marijuana exposure during pregnancy were evaluated within the baseline model, there was no appreciable change in the magnitude of the estimated cocaine effect on language performance. Only prenatal alcohol exposure was independently related to language functioning (p = .060) and retained in further modeling. As presented in Table 5, Model 3, the cocaine-related effect on language functioning remained stable with child's age and gender, and prenatal alcohol exposure retained the model (D = -0.124; CI = p = -0.241, -0.007; p = .037).

Analyses were also performed to check whether cocaine-associated language deficits might depend on varying levels of prenatal use of alcohol, tobacco, and marijuana by including product terms for each drug. The combination of prenatal cocaine and alcohol exposure did not indicate more pronounced language deficits (p = .894). Similarly, the combination of cocaine and marijuana exposure (p = .753) and cocaine and tobacco exposure (p = .274) did not appear to produce greater language deficits.

Mediating Influences of Fetal Growth and Gestational Age—Fetal growth indicators (birth weight, length, and head circumference) were evaluated as potential mediators. In separate models including the child's age as a covariate, language functioning was related to birth weight (p = .047) and length (p = .028) but not to head circumference (p = .558). However, as a result of multicollinearity among the three growth indicators, a composite index for fetal growth was created. A principal components analysis and internal consistency statistics confirmed that these measurements served well to index a single underlying dimension of fetal growth (Cronbach's alpha = 0.87). Consistent with the hypothesis of mediation, prenatal cocaine exposure was related to the composite index of fetal growth ($p < .001$), and in a separate model that included the child's age and gender, the fetal growth composite was related to language performance (p = .033). The relationship between prenatal cocaine exposure and

language functioning (Table 5, Model 1: D = -0.151; p = .012) was attenuated when the composite fetal growth dimension was added to the longitudinal regression model (Table 5, Model 4: D = -0.087; p = .172), indicating possible mediation of the cocaine-language relationship. Gestational age had no influence on language performance (p = .840) and was not evaluated further.

Child/Caregiver Characteristics—Characteristics assessed at the 3-year follow-up visit and evaluated within the baseline model included years in day care, years with biological mother as primary caregiver, hearing abnormalities (none, 1 ear, and 2 ears), and blood lead levels. Demographic birth variables (i.e., education, employment, and marital status) remained highly intercorrelated when reassessed at 3 years and were therefore not included a second time within the longitudinal model. Initial analyses indicated that none of the characteristics included from the 3-year visit met the confounding criteria. Child blood lead levels were related to language and retained for statistical modeling. Specifically, there was an association between the two highest lead exposure levels (15-19, p = .020; and 20-44, p < .001) and language performance, although a very small number of children accounted for this relationship (Table 4). As shown in Table 5, Model 5, there was no appreciable decrement in the estimated cocaine effect when lead levels were introduced into the longitudinal regression model already including child age, gender, and prenatal alcohol exposure (D = -0.152; CI = -0.273, -0.031; p = .014).

Child Cognitive Level—Child cognitive functioning measured at the 3-year visit was included in the model to assess the influence of prenatal cocaine exposure on language skills after taking into account the shared variation between cognition and language. The 3-year visit data were used because this was the first assessment in which separate measures were used to assess language and cognition. Covariates from the final longitudinal model (child age, gender, prenatal alcohol exposure, and blood lead levels) were included in two separate regression models. Consistent with the longitudinal results, prenatal cocaine exposure was associated with language functioning (D = 0.272; CI = -0.472, 0.073; p = .008) and remained independently related to language with inclusion of cognition in the model, although the effect estimate was somewhat attenuated (D = -0.197; CI = -0.338, -0.056; p = .006).

DISCUSSION

The Miami Prenatal Cocaine Study has numerous methodological strengths, including prospective study enrollment at birth and collection of detailed postnatal maternal interviews and biological markers (meconium and urine) to determine cocaine exposure status. The cohort is homogenous with regard to full-term gestation, race-ethnicity, and socioeconomic status. Examiners blinded to exposure status performed all assessments. Longitudinal analysis of multiple time points included evaluation of numerous potential confounding influences, including other prenatal substance exposures and analysis of fetal growth and gestational age as potential mediators.

This study's primary finding indicated a modest generalized language performance deficit associated with prenatal cocaine exposure in children evaluated at six time points from 4 months to 3 years of age. Children with prenatal cocaine exposure performed on average an estimated 15% of a SD lower on measures of global language ability when compared with non-cocaine-exposed children. Individual time-point analyses indicated these results were strongest for the 18-month and 3-year assessments, with estimated cocaine effects in the range of 25% of a SD unit, possibly as a result of increased measurement reliability achieved with the child's increasing age.

Studies of prenatal cocaine exposure have often drawn both substance-exposed and comparison groups from economically impoverished populations sharing many adverse conditions, making it increasingly important to consider cocaine-related effects within the context of other important health and social-environmental determinants of development. In the current study, the magnitude of the cocaine-associated difference in language functioning remained stable after evaluation of a number of potential confounding influences, including child age and gender, other substances used during pregnancy (alcohol, marijuana, and tobacco), prenatal care, maternal age, education, employment, marital status, child blood lead levels, hearing abnormalities, biological mother primary caregiving, and day-care attendance through 3 years of age. In addition, prenatal cocaine exposure remained a determinant of language functioning at 3 years of age after considering the shared variability between cognitive and language abilities.

Statistical adjustment for fetal growth, as measured by a composite of birth weight, length, and head circumference, resulted in attenuation of the cocaine-related effect on language. Analysis of the individual growth parameters indicated that birth weight and length accounted for these findings, although the significant degree of intercorrelation among the three measures of fetal growth supported their evaluation as a composite variable. The absence of a relationship between head circumference and language functioning indicates that language development was impacted by a more generalized deficit, perhaps associated with low birth weight and related risk factors as opposed to a specific deficit resulting from smaller head circumference. Although the findings overall indicate a potential mediating pathway involving fetal growth, the degree of mediation was modest in this full-term sample and in need of replication. A mediating influence may be more evident in a premature or more significantly growth-retarded sample. Gestational age was not related to language functioning in the current study of full-term infants but may play a more significant role in premature infants. Although sample size constraints limit the number of mediating influences that can be investigated, a focus on fetal growth was relevant because of findings of a cocaine-related intrauterine growth effect in several postnatal studies, often in the absence of other consistent findings.[10-18] In addition, previous studies have not typically investigated potential mediating pathways despite increased recognition that statistical control of potential mediators may obscure the influence of prenatal cocaine exposure.[60,61]

A number of subsidiary findings relevant to language functioning were also observed. Consistent with previous research, boys appeared to lag slightly behind girls in their language abilities, and prenatal alcohol use and higher lead levels at 3 years of age were also associated with poorer language functioning. Only 71% of the cocaine-exposed children remained in the care of their biological mother, compared with 97% of the non-cocaine-exposed children. Despite this difference, language abilities were not influenced and subgroup differences were not evident in relation to this caregiving factor. The rate of hearing abnormalities within each group was very low and did not influence the magnitude of the cocaine-associated language deficit. Language scores in both groups declined over time, from normative levels to average standardized scores less than 80 at 3 years of age in both groups. Clearly, other risk factors common to both study groups, such as low socioeconomic status and caregiver unemployment and lower educational attainment, may have adversely impacted the trajectory of language development. Although this trend was evident in both groups, children in the cocaine-exposed group exhibited even greater decrements, indicating an incremental risk for language development related to prenatal cocaine exposure. This finding appeared to be specific to language functioning and remained stable after consideration for the shared variability with general cognitive functioning, which was not similarly affected.

Results from the current investigation are consistent with an emergent pattern of findings suggestive of subtle language impairments in cocaine-exposed children evident during the

preschool years.[31-33,44,45,47] Given the small sample sizes characterizing many of these studies, results from the current larger, more rigorously controlled study represent increasingly reliable evidence suggestive of a cocaine-related influence on developing language skills. These findings are similarly supported by two more recent, well-controlled studies. Singer and colleagues[39] found children with heavier levels of cocaine-exposure performed more poorly on total language and auditory comprehension measures than children with lighter or no cocaine exposure. Delaney-Black and colleagues[48] reported cocaine-exposed children were 2½ times more likely to be categorized as low language functioning than their nonexposed peers at 6 years of age, although they did not find mean differences on individual standardized measures.

Several previous studies,[40-43] however, including a larger prospective study performed by Hurt and colleagues,[40] have not documented cocaine-related differences in language functioning. Although differences in research design and the selection of measures may account for these discrepant findings, it is also plausible that the larger sample size, high cohort retention rate, and longitudinal methodology used in the current study improved both the reliability of within-subject measurement and the ability to detect a stable but subtle pattern of language effects. This notion is further supported by the power calculations reported by Hurt and colleagues indicating that an effect size of 0.50 SD would have been necessary to ascertain differences, given a total sample size of 160.

Subtle differences in mean language scores between groups may have limited clinical significance at the level of the individual child, but the associated shift in population distributions can have considerable public health and societal ramifications.[27] A recent meta-analysis[27] demonstrated that effect estimates in the range of 26% of a SD unit for receptive language and 29% of a SD unit for expressive language resulted in approximately three- to four-fold increases in the numbers of children requiring special education services, with yearly costs estimated at 17 to 180 million dollars. In the current study, the .24 SD difference in mean language functioning at 3 years of age translated to 38.9% of the cocaine-exposed children falling below the typical clinical standardized cutoff score of 70 for service eligibility, as opposed to 27.8% of non-cocaine-exposed children. Although both groups had higher than expected percentages of children potentially in need of language remediation, cocaine-exposed children were clearly at increased clinical risk.

Several limitations and features of this study merit attention. The follow-up study cohort included only full-term infants and excluded infants with major congenital malformations, disseminated congenital infection, or HIV. Prenatal cocaine exposure may have a more clinically devastating influence on infants born prematurely or suffering from various medical conditions. The sample was restricted to African-American infants typically residing in disadvantaged inner-city neighborhoods. These sampling procedures promoted greater similarities between the groups with respect to important social and environmental determinants of development, increasing the ability to detect cocaine-related effects but limiting application of study results to other populations or settings. Although the present study used rigorous classification methods, including meconium screening to broaden the timeframe for detecting cocaine ingestion during pregnancy, misclassification errors may still have occurred and potentially biased estimates of the cocaine-effect toward the null hypothesis. Finally, the postpartum recruitment period did not allow for ongoing drug screening or documenting health information during prenatal visits.

Although standardized global assessments such as those used in the present study ensure common measurement practices for research purposes, standardized language tests do not sample all components of language and may not be sensitive to subtle variations in discourse, pragmatics, syntax, and semantics. Given the present evidence of a cocaine-related deficit in

global language abilities during early childhood, further investigation is needed to determine whether prenatal cocaine exposure exerts a differential influence on any specific components of language processing. Delineation of a cocaine-specific versus general influence on linguistic processing abilities, as well as other neuropsychological processes, will provide the groundwork for identifying possible cocaine-associated biological and environmental mechanisms that play a role in language development.

In summary, the current study reports supportive evidence for a subtle, consistent pattern of cocaine-associated deficits in language functioning measured over six intervals during the first 3 years of life. Prenatal cocaine exposure remained a stable determinant of language abilities after considering prenatal exposure to other drugs and important, social-environmental determinants. In a recent review, Frank and colleagues[62] suggested that there was no evidence to support a unique link between prenatal cocaine exposure and language functioning through 3 years of age on the basis of results summarized from three studies,[40,47,63] one in which the sample size was less than 25 participants.[47] Findings from the present study indicate that this conclusion may have been premature, having been drawn from an insufficient number of larger well-controlled studies.

Cocaine's causal mechanisms related to language are not well defined, although hypothesized pathways of influence include impaired neurobehavioral arousal and attention processes that are essential to processing linguistic cues and information, disruption to specific parent-child interactions critical to language development as a result of parental drug use, and the influence of the negative social environment typically associated with parental use of cocaine and other drugs.[46] It is difficult to separate the relative influence of prenatal cocaine exposure from associated postnatal influences, which are likely to be cumulative. In the present study, however, the absence of subgroup variation related to biological parenting indicated that the influence of cocaine on language functioning occurred independently of whether the child remained in the care of a biological parent with a potential substance use problem.

It is important to note that cocaine-exposed children may be at increased risk because of the postnatal child-rearing environments in which they are raised. The concept of “cumulative risk,” well established in developmental research, suggests that the total number of family risk factors, irrespective of the specific type of risk factor, combine to yield more complete predictions of long-term child outcome.[64,65] The present study, although more comprehensive than most in considering postnatal environmental influences, did not include consideration of such factors as ongoing parental substance abuse or the quality of the learning environment at home, both potentially important factors in understanding individual variation in cocaine-exposed children. Further study of these and other factors is needed to better understand both the prenatal and postnatal causative context in which the expression of cocaine-related effects occurs across the developmental continuum. Finally, the importance of early language development to later academic success, particularly in the areas of reading and writing, is well established.[29,30] Although the findings of the current study are subtle, cocaine-exposed children exhibited a consistent pattern of language deficits that may have important ramifications for long-term academic and social adaptation, particularly when taken into consideration within the broader context of other potential risk factors.

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Table 1

Self-Reported Alcohol, Tobacco, Marijuana, and Cocaine Use During Pregnancy

	Non-Cocaine-Exposed (n = 214)		Cocaine-Exposed (n = 250)	
Percentage and Number Endorsing Drug Use	**%**	**n**	**%**	**n**
Alcohol*	32	68	67	167
Tobacco*	17	37	73	183
Marijuana*	12	26	45	112
Cocaine			69	172

Total Pregnancy Use[a]	**Median**	**Min, Max**	**Median**	**Min, Max**
Alcohol (no. standard drinks)	54	2, 1680	96	1, 5226
Tobacco (no. cigarettes)*	1008	1, 5880	2380	1, 8820
Marijuana (no. joints)	28	1, 807	24	1, 1320
Cocaine (no. lines/rocks)			127	1, 19320

[a] Median values and comparisons based only on those mothers reporting usage, calculated using total exposure composites: (no. weeks used) × (usual no. of days per week) × (usual dose per day).

* $p \leq .01$.

Table 2

Means and Standard Deviations of Language Scores

	Language Score			Examination Age	
	Mean	**SD**	**Group n**	**Mean**	**SD**
BSID/Kent Language Score[a]					
4 Months					
Non-cocaine-exposed	76.7	26.6	152	4.2	0.5
Cocaine-exposed	77.0	27.9	171	4.2	0.4
8 Months					
Non-cocaine-exposed	97.6	15.7	159	8.1	0.6
Cocaine-exposed	95.6	16.9	176	8.1	0.6
12 Months					
Non-cocaine-exposed	97.9	12.8	176	12.1	0.8
Cocaine-exposed	97.3	13.2	205	12.1	0.8
18 Months					
Non-cocaine-exposed	95.5	12.4	189	18.1	0.7
Cocaine-exposed	91.9	14.2	224	18.1	0.8
24 Months					
Non-cocaine-exposed	87.5	11.1	194	24.1	0.8
Cocaine-exposed	86.0	12.4	231	24.0	0.8
3-Year CELF-P Total Standard Score[b]					
Non-cocaine-exposed	75.5	9.9	198	39.7	1.6
Cocaine-exposed	73.0	9.6	226	39.6	2.3

CELF-P, Clinical Evaluation of Language Fundamentals-Preschool; BSID, Bayley Scales of Infant Development; SD, standard deviation.

[a] Developmental age/chronological age × 100.

[b] CELF-P standard scores based on age norms (mean = 100; SD = 15).

Table 3

Maternal/Infant Characteristics at Birth (n = 464)[a]

	Non-Cocaine-Exposed (n = 214)		Cocaine-Exposed (n = 250)	
	Mean	**SD**	**Mean**	**SD**
Infant characteristics				
Birth weight (g)*	3291	492	2971	475
Birth length (cm)*	50.7	2.3	48.9	2.5
Birth head circumference (cm)*	33.8	1.4	33.0	1.6
Gestational age (wk)*	39.7	1.4	39.4	1.4
Boys (%, n)	50	106	50	124
Maternal characteristics				
Maternal age* (yr)	23.7	5.4	28.7	4.8
Number of prenatal visits*	10.0	6.8	7.3	6.2
Education (yr)	11.3	1.4	11.1	1.5
Received prenatal care (%, n)*	93	198	83	208
Never married (%, n)	89	191	90	225
Unemployed (%, n)*	83	178	95	237

[a] n = 464 based on completing at least one language assessment during the longitudinal period under study.

* $p \leq .01$.

Table 4

Caregiver and Child Characteristics at Three-Year Follow-Up Visit

	Non-Cocaine-Exposed			Cocaine-Exposed		
	%	n	Group, n	%	n	Group, n
Caregiver unemployed	63	128	204	71	166	233
Biological mother caregiver*	97	199	205	71	166	234
Child in day care*	34	69	205	52	122	234
Child lead level*			197			227
1-9	95	188		88	200	
10-14	4	8		10	22	
15-19	0.0	0		2	4	
20-44	0.5	1		0.4	1	
Child hearing			199			222
Abnormal one ear (%)	3.0	6		6	13	
Abnormal both ears (%)	3.0	6		3	6	

	Mean	SD	Group n	Mean	SD	Group n
Caregiver education (yr)	11.3	1.5	205	11.2	1.7	234
Years w/biological mother*	3.0	0.4	202	2.2	1.3	227
Years in Daycare (0-3)*	0.9	1.1	202	1.3	1.2	225
Child McCarthy GCI score	82.6	12.6	198	81.5	11.7	226

GCI, General Cognitive Index.

Numbers (n) reflect available covariate follow-up data for the subsample (n = 464) of children included in the longitudinal analysis who attended the 3-year follow-up visit.

* $p \leq .01$.

Table 5

Estimated Effects Under Several Longitudinal Model Specifications of Prenatal Cocaine Exposure on Language Development in Children Four Months through Three Years of Age

	Effect Estimate	95% CI	*p*
Model 1: Controlling for age at each assessment (n = 464)	-0.151	-0.269, -0.033	.012
Model 2: Subsumes Model 1 and adds a covariate term for infant gender (n = 464)	-0.150	-0.267, -0.033	.012
Model 3: Subsumes Model 2 and adds a covariate term for prenatal alcohol exposure (n = 464)	-0.124	-0.241, -0.007	.037
Model 4: Subsumes Model 3 and adds a covariate term for the fetal growth composite (n = 464)	-0.087	-0.213, 0.038	.172
Model 5: Subsumes Model 3 and adds covariate terms for child lead level (n = 415)	-0.152	-0.273, -0.031	.014

CI, confidence interval.