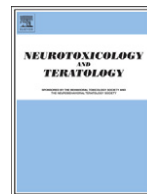




Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

The effects of prenatal cocaine on language development at 10 years of age

Barbara A. Lewis^{a,*}, Sonia Minnes^b, Elizabeth J. Short^c, Paul Weishampel^d, Suddida Satayathum^d, Meeyoung O. Min^d, Suchitra Nelson^e, Lynn T. Singer^{d,f}^a Department of Communication Sciences, Case Western Reserve University, Cleveland, OH 44106, United States^b Mandel School of Applied Social Sciences, Case Western Reserve University, Cleveland, OH, United States^c Department of Psychology, Case Western Reserve University, Cleveland, OH, United States^d Department of Pediatrics, Case Western Reserve University, Cleveland, OH, United States^e Department of Community Dentistry, School of Dentistry, Case Western Reserve University, Cleveland OH, United States^f General Medical Sciences, Case Western Reserve University, Cleveland, OH, United States

ARTICLE INFO

Article history:

Received 2 October 2009

Received in revised form 21 June 2010

Accepted 21 June 2010

Available online 30 June 2010

Keywords:

Cocaine

Lead

Language outcomes

Home environment

Gender

Tobacco

ABSTRACT

Objective: To examine the long term effects of prenatal cocaine exposure (PCE) on the language development of 10-year-old children utilizing a prospective design, controlling for confounding drug and environmental factors.

Participants: Children exposed to cocaine in utero (PCE; $n = 175$) and non-exposed children (NCE; $n = 175$) were followed prospectively to 10 years of age and were compared on language subscales of the Test of Language Development-Intermediate 3rd Edition (TOLD-I:3) and phonological processing as measured by the Comprehensive Test of Phonological Processing (CTOPP).

Methods: Multivariate analysis of covariance (MANCOVA), linear regression, and logistic regressions were used to evaluate the relationship of prenatal cocaine exposure to language development, while controlling for confounders.

Results: After controlling for confounding variables, prenatal cocaine effects were observed for specific aspects of language including syntax (Sentence Combining subtest of the TOLD-I:3, $p = 0.001$), semantics (Malopropism subtest of the TOLD-I:3, $p = 0.05$) and phonological processing (Phonological Awareness subscale, $p = 0.01$). The caregiver factors of vocabulary, HOME, and psychological symptoms also had consistent effects on language subtests and phonological processing scores. Children with PCE who experienced foster or adoptive care had enhanced language development compared to those living with birth mothers or in relative care. Cocaine exposed girls had lower scores on the phonological awareness subscale of the CTOPP than non-exposed girls.

Conclusions: PCE has subtle effects on specific aspects of language development and phonological processing at age 10, even after controlling for confounding variables. Environmental factors (i.e., postnatal lead exposure, home environment, and caregiver vocabulary and psychological symptoms) also impact language skills at 10 years. Adoptive or foster care appears to enrich PCE children's linguistic environment and protects children against language delay in the PCE sample.

© 2010 Elsevier Inc. All rights reserved.

1. Introduction

Language functioning of children with prenatal cocaine exposure (PCE) is of particular interest to researchers, clinicians, and educators both because of the relationship of early language skills to cognitive

development and due to the relationship of language deficits to later reading skills and subsequent academic and social success. While some prospective studies have not found PCE effects on language [3,25], the majority of studies of preschool children with PCE have reported both receptive and expressive language deficits, as well as subtle deficits in specific language domains such as phonology, semantics, syntax, and pragmatics [2,4,12,15,21,27,33,41].

Language delays of children with PCE in early childhood have been assumed to be related to both biologic risk and postnatal environmental influences. Biological risks include a disruption in attentional processing related to prenatal drug exposure [23,36,39,42]. Environmental risks stem from inadequate stimulation provided by a drug using mother [32,45], insecure child attachment [38], caregiver's verbal abilities [27] and a variety of factors associated with poverty [8]

Abbreviations: CE, cocaine exposed; NCE, non-cocaine exposed; BZE, benzoyllecgonine; M-OH-BZE, meta-hydroxybenzoyllecgonine; TOLD-I:3, Test of Language Development-Intermediate, 3rd Edition; CTOPP, Comprehensive Test of Phonological Processing; PPVT-R, Peabody Picture Vocabulary Test-Revised; WAIS-R, Wechsler Adult Intelligence Scale-Revised; BD, block design; PC, picture completion; BSI, Brief Symptom Inventory; GSI, General Severity Index; HOME, Home Observation for Measurement of the Environment; SES, socio-economic status.

* Corresponding author. Tel.: +1 216 368 4674 (office); fax: +1 216 368 6078.

E-mail address: bxl@case.edu (B.A. Lewis).

including exposure to environmental toxins such as lead. Several prospective studies of children with PCE have found stable cocaine specific effects on composite receptive, expressive and total language scores, even after control for multiple medical and demographic covariates during early childhood (birth to 6 years), a time of rapid spoken language acquisition [2,33].

In the longitudinal Miami Prenatal Cocaine Study that examined language development across 6 time points from 4 months to 3 years of age, Morrow et al. [33] reported that children with PCE had overall lower language scores than children who were not cocaine exposed (NCE). Cocaine effects were strongest at the 18 months and 3 years assessments, possibly due to more reliable assessments at this age. Morrow further contended that deficits in fetal growth (i.e., birthweight, length, and head circumference) were related to cocaine exposure, with these deficits mediating language differences between the groups. Additional individual differences were noted by the Miami group, with boys lagging behind girls and additional substance exposure (i.e., alcohol and lead) at 3 years associated with poorer language outcomes. Non-biological care was not found to influence language outcomes. Language outcomes were reported to decline with age. A subsequent report on the Miami cohort at 3 years of age, Morrow et al. [34] found a similar gradient relationship between the degree of cocaine exposure and decreased expressive language skills to our Cleveland cohort's early findings [41]. Receptive language skills of children with PCE were not significantly different from non-exposed children. Bandstra et al. [2] reported on additional longitudinal language findings of the Miami cohort at 3, 5, and 7 years of age. The Clinical Evaluation of Language Fundamentals-Preschool (CELF-P) was administered at 3 and 5 years and the core language domain of the NEPSY at 7 years. An association of PCE and total language functioning was found after controlling for multiple medical and socio-demographic variables. However, at the 7 years assessment, these language deficits did not appear to be related to deficits in fetal growth as was suggested in their earlier reports.

In our previous studies of the cohort reported on in the current paper, we found deficits in auditory processing of children with PCE at 1 year of age [41]. At the 4 years assessment, we reported significant differences in expressive and total language scores but not in receptive language scores, with children with PCE scoring more poorly than controls [27]. When children were classified based on language scores below a standard score of 85, children with PCE were more likely to have delays in receptive language than non-exposed children. Examination of this cohort longitudinally at 1, 2, 4, and 6 years of age employing random coefficient modeling while controlling for confounders showed a significant stable, longitudinal effect of cocaine exposure on language, with children with PCE demonstrating greater overall linguistic deficits compared to non-exposed children and a more dramatic decline in language performance over time [26].

Although early childhood language deficits of children exposed to cocaine have been documented, few studies that have examined the effects of PCE on language in the elementary school years. During the school years new demands are placed on language skills, as the child learns to read and write. Spoken and written language skills are crucial for children's successful social and academic competence [4]. Prenatal cocaine exposure may affect brain regions associated with higher linguistic skills that are more appropriately assessed at school age [4].

In one of the first studies to examine children with PCE beyond 7 years of age, Beeghly [4] examined 160 children in a prospective study at 6 years and 9.5 years of age on a standardized language assessment (TOLD-P:3 at 6 years and the CELF-3 at 9.5 years.). Age, birthweight and gender were found to moderate the relationship between PCE and language outcomes. Children with PCE had lower receptive scores at 6 years but not at 9.5 years if they had lower birth weights. Lower expressive and total language scores were reported

for children with PCE at both time points if they were female [4]. As reported in their previous work [3,16] no significant main effects of PCE were found for composite scores on a variety of language measure. Use of composite scores of language in standardized testing is a common practice; however the effects of specific language processing skills, such as syntax, semantics, pragmatics, and phonological processing, often are missed when composite scores are utilized. These skills may be differentially affected by prenatal cocaine exposure.

Several studies have examined specific language domains such as pragmatic skills [30], semantics [7], and phonology [29]. A large prospective cohort study conducted by Delaney-Black et al. [12] on 6-year-old children examined in great detail articulation and language skills of children with PCE. Data from a spontaneous language sample were analyzed for specific linguistic skills, including such things as communication units (C-unit) and type-token ratios (number of word types per number of words; TTR). While significant differences of mean C-units and TTR by cocaine-exposure group were not observed, children with PCE were 2.4 times more likely to be in the experimentally defined low language group than control children after adjustment for covariates. A language threshold was hypothesized by these researchers in which a combination of biological and environmental factors is likely to place children with PCE in the low language group. These findings were in agreement with a previous report that children with language delays were more likely to have PCE than children with normal language development [1].

Inconsistencies in language findings to date of children with PCE suggest that studies employing large longitudinal prospective cohorts and examining specific language domains are needed to clarify the relationship of PCE to language skills. Further, studies need to be extended into school age to document the effects of PCE on more complex linguistic skills that may impact academic outcomes. The present investigation was designed to examine specific language domains and extend our previous studies of PCE into the school age years. Specific domains of higher level linguistic skills including semantics, syntax, and phonological processing were examined. Careful control of environmental factors known to relate to child language skills was completed, with special attention directed to caregiver's vocabulary and psychological symptoms, placement in foster/adoptive care, and environmental lead exposure. Based on our previous findings and those reported in the literature, our specific hypotheses were:

1. Children with PCE will perform more poorly than children without exposure on specific language skills.
Children with PCE in our cohort have presented with poorer language skills at 1, 4, and 6 years of age. We have found that language skills have declined with age and children with PCE have not caught up to their NCE peers. Thus, we predicted that at 10 years, poor language skills will be evident, with specific linguistic skills (i.e. syntax and semantics) greatly impacted.
2. Children with PCE will perform more poorly than children without exposure on measures of phonological processing, especially the phonological awareness, phonological memory and rapid automatized naming subscales of the CTOPP.
We predicted that children with PCE will also demonstrate poorer phonological processing skills tapped by these subtests strongly related to reading skills. Our early findings showed deficits in auditory processing that may be related to these later phonological processing skills.
3. Children with PCE in adoptive/foster care will present with better language and phonological processing skills than children who remain in biological relative care.

Our previous research showed that children with PCE in adoptive/foster care demonstrate better language skills than children in

biological relative care. We expected that this finding would persist at the 10 year follow-up.

2. Methods

2.1. Subjects

Three hundred and fifty children (175 with prenatal cocaine-exposed (PCE) and 175 non-exposed, (NCE)) were followed prospectively from birth at 1, 2, 4, 6, and 9 years and assessed for language development at 10 years of age. The sample was drawn from a cohort recruited at birth (September 1994–June 1996) from a large, urban, county teaching hospital and had participated in a longitudinal study of the sequelae of fetal drug exposure. IRB approval from University Hospitals of Cleveland and MetroHealth Medical Center was obtained for all participants, with informed consent obtained from parents and assent obtained from the youngster. Health Insurance Portability & Accountability Act of 1996 (HIPAA) was maintained. All subjects were protected by a writ of confidentiality (DA-04-03) preventing the release of any subject information from the research even under court order.

Women considered high risk for drug use due to lack of prenatal care, behavior suggesting intoxication, a history of involvement with the Department of Human Services or self-admitted use were administered drug toxicology screenings at the child's birth. Maternal and infant urine samples were obtained immediately before or after labor/delivery and analyzed for the presence of cocaine metabolites (benzoylecgonine), cannabinoids, opiates, PCP, and amphetamines. In addition, infants had meconium drug analyses performed for cocaine and its metabolites (i.e. benzoylecgonine (BZE), meta-hydroxybenzoylecgonine (M-OH-BZE), cocaethylene, cannabinoids (THC), opiates, PCP, amphetamines, and benzodiazepines). Screening assays were conducted using polarization immunoassay reagents (fluorescence polarization immunoassay; US Drug Testing Laboratories, Inc, Des Plaines, IL). Cutoff levels were as follows: cocaine and metabolites, opiates, 25 ng/g; amphetamines, 100 ng/g; phencyclidine, 25 ng/g; tetrahydrocannabinol, 25 ng/g. Confirmatory assays were conducted. Specificity for both urine and meconium cutoffs was 99%.

Infants with PCE were identified based on either positive infant meconium, maternal urine, or maternal self-report, while control infants were negative on all three indicators. Women who used alcohol, marijuana, or tobacco during pregnancy were included in both groups. Of the 647 mothers identified, 54 were excluded (20 PCE and 34 NCE) from this study, with 15 not having meconium, 2 having Down syndrome, 16 having maternal psychiatric history, 2 due to primary heroin use, 5 having human immunodeficiency virus status, 1 due to IQ < 70, 1 having fetal alcohol syndrome, 2 due to maternal age under 19 years, 3 due to a medical illness in the infant, 4 due to chronic illness in the mother, and 3 for other reasons. Additionally, a total of 155 women (49 cocaine using and 106 non-cocaine using) refused to participate; and 23 (9 PCE and 14 NCE) did not come to the enrollment visit. The sample size of the original cohort was 415 (218 PCE, 197 NCE). By age 10 years, 11 of the children in the study group (8 PCE and 3 NCE; $\chi^2 = 1.9$; $p < 0.17$) had died. Of the 54 children not seen, the 35 PCE children were more likely to be Caucasian, to have had higher birth weight, and to have mothers with lower WAIS-R picture completion scores compared with the study participants, and the 19 NCE children had lower alcohol exposure compared with the participants.

It should be noted that at 2 and 4 years of age, a subgroup of children participated in a separate study of lead exposure. Venous blood samples could not be obtained from some children due to lack of parental consent, excessive stress related to the blood draw, child illness, or logistic difficulties. The number of children followed at 10 years with valid blood measurements at 2 and 4 years were 133 and 258 respectively (275 total children with blood measurements). For the 116 children with blood measurements at both times, the

values were averaged. The subgroup of participants with lead levels differed from the total sample in that there were more African-Americans and married parents and fewer adoptive/foster care parents, had more prenatal care, lower levels of average prenatal cigarette exposure, and larger head circumference. Continuous blood lead values were used in the statistical analyses.

2.2. Procedures

To assess prenatal drug exposure, infants and their birth mothers were seen immediately after birth, at which time, the birth mother was interviewed regarding drug use. Birth mothers were asked to recall the frequency and amount of drug use for the month prior to pregnancy, and each trimester of her pregnancy. Additionally, for tobacco, the number of cigarettes smoked per week was recorded; for marijuana, the number of joints smoked per week; for alcohol, the number of drinks of beer, wine, or hard liquor per week was computed (with each drink equivalent to 0.05 oz. of absolute alcohol); and for cocaine, the number of rocks consumed and amount of money spent per week were noted. For each drug the frequency of use was recorded. This drug assessment was updated at each follow-up visit to provide a similar measure of current drug use, with the assessments also administered to the foster or relative caregiver to provide a measure of caregiver postnatal environmental use.

Birth, demographic, and medical characteristics were taken from hospital records, including maternal race, age, parity, number of prenatal care visits, type of medical insurance, infant Apgar scores, and infant birthweight, length, and head circumference. At enrollment into the study, maternal socio-economic status [20] and educational level were calculated. Maternal vocabulary score was measured using the Peabody Picture Vocabulary Test-Revised (PPVT) [14]. Two performance subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [48] were administered: The Block Design (BD) and Picture Completion (PC) subtests which enabled an estimate of non-verbal intelligence. The Brief Symptom Inventory (BSI) [13] is a standardized self-report scale that was administered at birth and at all visits to obtain a measure of severity of psychological distress. The General Severity Index (GSI) a summary score of the BSI was used as an indicator of overall distress. The Hobel Neonatal Risk Index [19] was computed to obtain a measure of neonatal medical complications. At the 10 years visit, the child's placement (either birth mother/relative or foster/adoptive caregiver) was noted and data on the current caregiver were updated. If the child had been placed with a new caregiver, intellectual measures of the caregiver were also updated. The Home Observation of the Environment (HOME) [9] was administered to the caregiver in an interview format as a measure of the quality of the caregiving environment at each visit. The HOME was administered in the laboratory as suggested by Jacobson and Jacobson [22] (1995). The HOME total score at 10 years of age was utilized in our analyses.

2.3. Language and phonological processing measures at 10 years

At 10 years of age, examiners unaware of the children's cocaine or lead level status individually administered the Test of Language Development-Intermediate 3rd Edition (TOLD-I:3) [18] and the Comprehensive Test of Phonological Processing (CTOPP) [46]. The TOLD-I:3 assesses the understanding and meaningful use of spoken words, as well as different aspects of grammar. The test is comprised of 6 subtests including sentence combining, picture vocabulary, word ordering, generals (identifying super ordinate categories for words), grammatical comprehension and malapropisms (identifying words that sound alike but have different meanings). Age standardized scores were computed for subtests. In an effort to precisely identify which specific linguistic domains were affected, subtest scores rather than composite scores were employed. The composite scores of the TOLD-I:3 are formed

from the subtest scores and a single subtest score is employed to create multiple composite scores. Due to this overlap of subtests in the composite scores, we choose not to examine composite scores of the TOLD-I:3. The composite scores of the CTOPP do not overlap and thus were examined. The CTOPP assesses Phonological Awareness (i.e. a composite score of the Elision and Blending Words subtests), Phonological Memory (i.e. a composite score of the Memory for Digits and Nonwords subtests), and Rapid Naming (i.e. a composite score of the Rapid Naming of colors, objects, digits, and letters subtests). Difficulties in one or more of these domains of phonological processing abilities may adversely affect difficulty person's ability to read. Age standardized scores are available for each of the three subscales and five subtests (Elision, Blending Words, Memory for Digits, Nonwords, and Rapid Naming) of the CTOPP.

2.4. Statistical analysis strategy

Baseline maternal characteristics, child characteristics, and prenatal drug exposure were summarized using means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Comparisons between PCE and NCE groups were performed using *t*-tests, Wilcoxon rank sum, and Pearson Chi-square tests. All positively skewed data, including drug self-report measures and GSI, were transformed using the natural logarithm of (*X* + 1) to achieve a distribution that approximates normality. Correlations between drug exposure data and language outcomes were estimated using Spearman correlation coefficients.

In order to reduce the possibility of spurious effects associated with multiple comparisons, we performed 2 separate MANCOVAs (i.e. one utilizing the six subtest scores of the TOLD-I:3 and one using the three subscales of the CTOPP) controlling for HOME score, current caregiver's psychological distress, and current caregiver's vocabulary (PPVT). These variables were chosen as covariates as they have been related to cognitive functioning in our previous work and are hypothesized to influence language development.

Multiple linear and logistic regression analyses were performed only on the outcomes that were significant (*p* < 0.1) in the MANCOVAs of the TOLD-I:3 and CTOPP and were correlated with language measures (*p* < 0.20) and different by cocaine status (*p* < 0.20). Covariates were entered into the regression model stepwise and were retained if, on entry, they were significant at *p* < 0.10 or caused substantial change (>10%) in the cocaine coefficient [31]. Environmental and prenatal factors were considered first, followed by demographic and drug exposure variables in the following order: cocaine exposure, HOME score, birth mother and current caregiver PPVT standard score, WAIS-R BD and WAIS-PC scores, maternal age at child's birth, parity, number of prenatal care visits, marital status, socio-economic status, birth mother and current caregiver GSI, and prenatal and current caregiver measures of cigarette, alcohol, marijuana and current child placement (non-relative foster/adoptive care vs. relative care) and blood lead level. Child's race and gender were tested as moderators of prenatal cocaine effects. Adjusted language scores controlling for confounding variables demonstrated to be significant in the regression model, were calculated to compare the cocaine-exposed and non-exposed groups. Logistic regression was employed to examine the bivariate language classification of <85 or >85.

3. Results

3.1. Sample characteristics

Cocaine using women and controls were primarily African-Americans, of low-income and not married (see Table 1). Cocaine using women were older, had more children, and received fewer prenatal care visits than controls. They used other drugs (i.e. alcohol, marijuana and tobacco) more frequently and in higher amounts than

Table 1
Maternal demographic characteristics by cocaine status.

Maternal demographics	Non-cocaine exposed (<i>n</i> = 175)		Cocaine exposed (<i>n</i> = 175)	
	Mean	SD	Mean	SD
Mother's age at birth ^a	25.54	4.81	29.77	4.94
Number of prenatal visits ^a	8.89	4.84	5.17	4.55
Parity ^a	2.71	1.88	3.46	1.84
Education (years) ^a	11.97	1.44	11.58	1.70
PPVT standard score ^a	78.16	14.70	73.93	15.57
Block design scale	7.21	2.11	6.89	2.11
Picture completion scale	7.03	2.37	6.71	2.14
Global Severity Index ^a	0.50	0.53	0.82	0.75
Average substance use				
Tobacco (cigarettes/day) ^a	4.01	7.48	11.70	10.84
Alcohol (dose/week) ^a	1.33	4.44	10.17	18.14
Marijuana (dose/week) ^a	0.64	3.59	1.38	3.56
Cocaine (units/week)	0.00	0.00	25.28	47.61
	<i>n</i>	%	<i>n</i>	%
Married ^a	28	16.00	15	8.57
African-American	142	81.14	146	83.43
Employed ^a	36	20.69	11	6.32
Low socio-economic status	171	97.71	171	98.28

^a Cocaine vs. non-cocaine statistically significant at *p* ≤ 0.05.

non-users. PCE infants were more likely to be preterm and of lower birth weight, head circumference (employed as a mediator of the cocaine effect), and birth length than NCE infants (see Table 2). At birth, 49 (26%) PCE infants were placed outside birth mother/relative care compared to only 3 (2%) of NCE infants (*p* < 0.05). By 10 years, 39 (22%) PCE children were in adoptive/foster care compared to 7 (4%) of NCE children ($\chi^2 = 25.6$; *p* < 0.001). Among the 136 children not in adoptive/foster care with PCE, 93 (53.14%) were with the biological mother, while 43 (27.43%) were in relative care. See Table 3 for a summary of current caregiver demographics.

3.2. Effects of prenatal drug exposure on language outcomes at 10 years

The MANCOVA for the 6 subtests scores of the TOLD-I:3 was significant at the *p* < 0.10 level (Wilks' Lambda = 0.96, *F* = 2.05, *df* = 3305, *p* = 0.059). When the scores for the entire sample were

Table 2
Child demographic and medical characteristics.

Child demographics	Non-cocaine exposed (<i>n</i> = 175)		Cocaine exposed (<i>n</i> = 175)	
	Mean	SD	Mean	SD
1 min Apgar	7.89	1.69	7.96	1.45
5 min Apgar	8.78	0.72	8.77	0.67
Gestational age (weeks) ^a	38.48	2.86	37.70	2.92
Hobel total	6.01	16.12	7.86	17.10
Baby length (cm) ^a	49.12	3.75	47.22	4.10
Head circumference (cm) ^a	33.46	2.41	32.21	2.18
Birthweight (g) ^a	3103.21	710.27	2680.13	655.63
Lead values at 2 and/ or 4 years-old ^a	8.12	4.63	7.18	4.06
	<i>n</i>	%	<i>n</i>	%
Male	82	46.86	76	43.43
African-American	141	80.57	146	83.43
Microcephalic ^a	8	4.62	25	14.45
Small birth size ^a	4	2.30	23	13.37
Child's age at 10 years.	10.11	0.17	10.13	0.19

^aLead sub-sample consisted of 138 NCE and 137 CE children.
^a Cocaine vs. non-cocaine statistically significant at *p* ≤ 0.05.

Table 3
Caregiver and child characteristics at 10 years by caregiver placement status.

Current caregiver demographics (10-years)	CE–birth mother/relative		CE–adopted/foster		NCE	
	(n = 136)		(n = 39)		(n = 175)	
	Mean	SD	Mean	SD	Mean	SD
Home score ^{a,b}	42.03	7.33	44.87	5.25	44.03	6.17
Education (years) ^{a,b,c}	11.85	1.78	13.72	2.72	12.58	1.76
PPVT standard score (verbal IQ) ^{a,c}	76.12	14.08	91.18	15.46	79.33	15.23
Block design scale (WAIS-R)	6.78	2.07	7.15	2.76	7.27	2.11
Picture completion scale (WAIS-R)	6.94	2.22	7.08	3.06	7.06	2.37
Global Severity Index (BSI) ^{a,c}	0.36	0.41	0.19	0.22	0.36	0.47
Average cigarettes/day ^{a,b}	6.77	8.12	2.03	5.50	3.09	5.60
Average alcohol dose/week	1.70	5.26	0.85	2.82	1.08	2.42
Average marijuana dose/week	0.43	2.95	0.00	0.00	0.07	0.40
Average cocaine units/week	0.71	6.62	0.00	0.00	0.00	0.00
Child lead levels at 2 and/or 4 years-old ^{a,c}	7.61	4.19	5.06	2.41	8.11	4.63
Lead ≥ 10 µg/dL (n, %)*	25	21.93	0	0	37	26.81
Prenatal substance exposure						
Average cigarettes/day ^{b,c}	11.14	10.56	13.70	11.73	4.01	7.48
Average alcohol dose/week ^{b,c}	8.94	15.42	14.51	25.34	1.33	4.44
Average marijuana dose/week ^b	1.36	3.24	1.44	4.58	0.64	3.59
Average cocaine units/week	22.83	39.21	33.82	69.42	0.00	0.00

*Lead sub-sample consisted of 114 CE–birth mother/relative, 23 CE–adopt/foster, and 138 NCE children.

^a CE–birth mother/relative vs. CE–adopted/foster care, $p \leq 0.05$.

^b CE–birth mother/relative vs. NCE, $p \leq 0.05$.

^c CE–adopted/foster care vs. NCE, and $p \leq 0.05$.

adjusted for significant covariates, cocaine effects remained significant for the Sentence Combining and Malapropism subtests of the TOLD-I:3 (Table 4 shows adjusted means). Effect sizes were small to moderate (0.31 for Sentence Combining).

The overall MANCOVA of the three subscales from the CTOPP was significant at the $p < 0.001$ level (Wilks' Lambda = 0.95, $F = 5.78$, $df = 3305$, $p = 0.0007$). An ANCOVA was conducted on each of the subscale scores of the CTOPP to further identify skills with a significant cocaine effect. The analysis of on the Phonological Awareness subscale revealed a significant effect for cocaine (Wilks Lambda = 0.97, $F = 4.49$, $df = 2307$, $p = 0.012$). Cocaine effects were not obtained for Phonological Memory or Rapid Naming ($p > 0.10$). Regression analyses were performed only on the outcomes that were significant on the overall MANCOVA. When the scores for the entire sample were adjusted for significant covariates, cocaine effects remained significant for the Phonological Awareness subscale and Elision subtest of the CTOPP. Effect sizes were small to moderate (0.30 for Elision).

There was a gender by cocaine interaction on the Phonological Awareness subscale and the Elision subtest, with cocaine exposed females performing more poorly than NCE females (Fig. 1). Logistic regression was employed to examine the bivariate language classification of < 85 or > 85 . There was a gender interaction in the logistic regression with the results only significant for girls. Seventy three percent of cocaine exposed girls had Phonological Awareness score < 85 compared to 53% of non-cocaine exposed girls ($p < 0.05$). There were no language difference observed between cocaine exposed boys (64%) and non-exposed boys (71%).

3.3. Effects of caregiver and environmental characteristics

See Table 5 for the bivariate correlation of the language outcomes with maternal and caregiver characteristics. The HOME score was significantly related to the Rapid Naming ($\beta = 0.16$, $p = 0.006$) subtests of the CTOPP and the Sentence Combining ($\beta = 0.12$, $p = 0.03$), Picture Vocabulary ($\beta = 0.15$, $p = 0.008$), Generals

Table 4
Adjusted language mean (SE) scores at 10 years.

	Cocaine exposed (n = 175)	Non-cocaine exposed (n = 175)	p value
<i>CTOPP</i>			
Phonological Awareness ¹	79.51 (1.05)	81.74 (0.99)	0.01
Elision ²	6.87 (0.26)	7.30 (0.25)	0.01
Blending Words ³	6.27 (0.18)	6.72 (0.18)	0.11
Phonological Memory ⁴	88.72 (1.20)	91.29 (1.15)	0.15
Rapid Naming ⁵	94.78 (1.19)	93.07 (1.16)	0.31
<i>TOLD-I:3</i>			
Sentence Combining ⁶	6.28 (0.23)	7.34 (0.22)	0.001
Picture Vocabulary ⁷	7.40 (0.23)	7.39 (0.20)	0.99
Generals ⁸	7.10 (0.23)	7.56 (0.20)	0.17
Grammatical Comprehension ⁹	7.47 (0.21)	7.90 (0.19)	0.17
Word Ordering ¹⁰	6.47 (0.30)	6.68 (0.26)	0.64
Malapropisms ¹¹	6.69 (0.22)	7.31 (0.19)	0.05

Note. Significant ($p < 0.05$) covariates are listed in italics.

¹ Adjusted for parity, maternal marital status, current caregiver's PPVT-R, current caregiver's global severity index, maternal alcohol dose per week 3rd trimester, child sex, and interaction of sex and cocaine status.

² Adjusted for parity, maternal marital status, maternal block design scale, current caregiver's global severity index, maternal cigarette use per day average, maternal alcohol dose per week average, child sex, and interaction of sex and cocaine status.

³ Adjusted for HOME score, parity, maternal marital status, current caregiver's PPVT-R, maternal number of cigarettes 2nd trimester, and maternal alcohol dose per week average.

⁴ Adjusted for current caregiver cigarettes use average, maternal alcohol dose per week average, and maternal marijuana dose per week 1st trimester.

⁵ Adjusted for HOME score, parity, and current caregiver cigarettes use average.

⁶ Adjusted for HOME score, parity, current caregiver's PPVT-R, current caregiver's global severity index, maternal marijuana dose per week month prior.

⁷ Adjusted for HOME score, parity, years of maternal education, current caregiver's PPVT-R, current caregiver's block design scale, current caregiver's global severity index, maternal alcohol dose per week average, and maternal marijuana dose per week 1st trimester.

⁸ Adjusted for HOME score, parity, years of maternal education, maternal PPVT score, current caregiver's block design scale, current caregiver's global severity index, maternal alcohol dose per week average, maternal marijuana dose per week 1st trimester, and foster/adoptive caregiver.

⁹ Adjusted for parity, years of maternal education, current caregivers PPVT-R, maternal block design scale, current caregiver's global severity index, maternal alcohol dose per week average, foster/adoptive caregiver.

¹⁰ Adjusted for parity, maternal marital status, current caregiver's PPVT-R, current caregiver's block design scale, current caregiver's global severity index, maternal cigarettes dose per day average, maternal average alcohol dose per week.

¹¹ Adjusted for HOME score, parity, years of maternal education, maternal marital status, maternal PPVT score, current caregiver's block design scale, maternal number of cigarettes 2nd trimester, and foster/adoptive caregiver.

($\beta = 0.16$, $p = 0.006$), and Malpropisms ($\beta = 0.16$, $p = 0.025$) subtests of the TOLD-I:3. Caregiver's vocabulary on the PPVT-R and psychological symptoms on the GSI impacted language skills at 10 years. GSI scores negatively related to Word Ordering subtests ($\beta = 0.114$, $p = 0.046$) of the TOLD-I:3. Lower current caregiver's PPVT-R scores were related to lower child scores on the Phonological Awareness ($\beta = 0.15$, $p = 0.046$) and Blending Words ($\beta = 0.14$, $p = 0.013$) subtest of the CTOPP and Picture Vocabulary ($\beta = 0.30$, $p < 0.0001$), Generals ($\beta = 0.22$, $p < 0.0001$), and Word Ordering ($\beta = 0.16$, $p = 0.008$).

Cigarette smoking in the second trimester of pregnancy was related to poorer language outcomes on the Malpropism subtests ($\beta = 0.15$, $p = 0.02$) of the TOLD-I:3 and the Blending Words ($\beta = 0.18$, $p = 0.008$) and Rapid Naming ($\beta = 0.15$, $p = 0.01$) subtests of the CTOPP.

Significant lead effects were found on Phonological Awareness ($\beta = -0.19$, $p = 0.0026$), Elision ($\beta = -0.21$, $p = 0.0009$), Sentence Combining ($\beta = -0.13$, $p = 0.0493$), Picture Vocabulary ($\beta = -0.15$, $p = 0.016$), and Grammatical Comprehension ($\beta = -0.13$, $p = 0.038$).

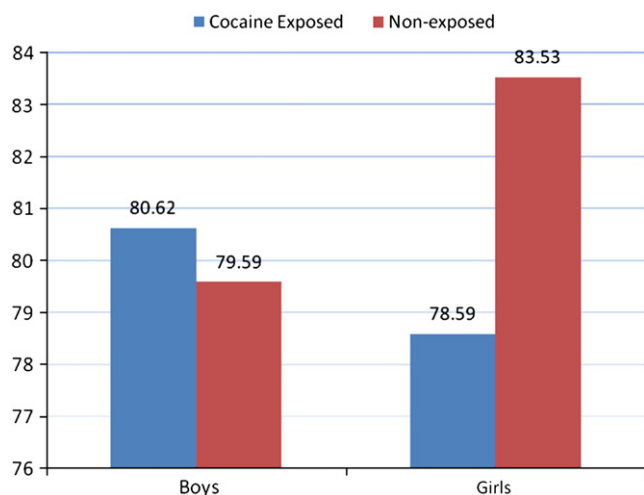


Fig. 1. Adjusted mean score of CTOPP Phonological Awareness by Cocaine Status and Gender, controlled for parity, maternal marital status, current caregiver's PPVT-R, current caregiver's global severity index, maternal alcohol dose per week 3rd trimester. Cocaine exposed girls had a lower Phonological Awareness score than non-cocaine exposed girls ($p=0.013$).

The cocaine effect on language and Phonological Awareness was not dramatically changed due to lead. With lead in the model, cocaine effects are $\beta = -0.15$, $p = 0.08$ on Phonological Awareness, $\beta = -0.21$, $p = 0.02$ on Elision subtest, and $\beta = -0.15$, $p = 0.0234$ on Sentence Combining subtest.

3.4. Adoptive/foster care versus birth mother/relative care

Within the PCE group children placed in adoptive/foster care were compared to children who remained in birth mother/relative care. Children with PCE in adoptive/foster care had significantly higher language outcomes than children with PCE in birth mother/relative care even after controlling for the effects of lead, HOME, PPVT, and GSI for the following outcomes: The Generals subtest of the TOLD-I:3 (Adjusted mean = 7.95 (SE = 0.41) of PCE in adoptive/foster care vs. 6.82 (0.18) of PCE in birth mother/relative care, $p = 0.016$), Grammatic Comprehension (8.76 (0.42) vs. 7.21 (0.19), $p = 0.002$), and Malapropisms (8.02 (0.43) vs. 6.64 (0.20), $p = 0.016$) subtests of the TOLD-I:3.

Table 5

Bivariate correlation of language outcomes with maternal characteristics. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

	HOME score	Parity	Education (years)	PPVT score	Block design scale	Global Severity Index	Average substance use during pregnancy		
							Tobacco (cigarettes/day)	Alcohol (dose/week)	Marijuana (dose/week)
<i>CTOPP</i>									
Phonological Awareness	0.07	-0.16**	0.06	0.16**	0.22***	-0.004	-0.04	-0.17**	-0.02
Elision	0.04	-0.18***	0.07	0.13*	0.22***	-0.02	-0.10	-0.18**	-0.02
Blending Words	0.09	-0.07	0.03	0.14*	0.42**	0.01	0.07	-0.09	-0.01
Phonological Memory	0.05	-0.06	0.01	0.03	-0.01	-0.03	-0.01	-0.09	0.04
Digits	0.02	-0.06	-0.02	0.03	-0.008	-0.07	-0.03	-0.02	0.08
Non word Repetition	0.05	-0.04	0.08	0.06	0.01	0.03	-0.003	-0.18**	-0.04
Rapid Naming	0.09	0.11*	0.02	-0.05	-0.04	0.07	0.05	0.03	0.0001
Digits	0.09	0.12*	0.02	-0.06	-0.06	0.08	0.04	0.04	0.005
Letters	0.10	0.09	0.02	-0.03	-0.03	0.05	0.04	0.008	-0.005
<i>TOLD-I:3 subtests</i>									
Sentence Combining	0.11*	-0.12*	0.09	0.19***	0.15**	-0.061	-0.12*	-0.12*	0.06
Picture Vocabulary	0.13*	-0.23***	0.16**	0.29***	0.23***	-0.05	0.04	-0.13*	0.06
Generals	0.13*	-0.18***	0.16**	0.24***	0.21***	-0.10	-0.02	-0.16**	0.06
Grammatic Comprehension	0.07	-0.10	0.19***	0.14*	0.20***	-0.05	0.03	-0.07	-0.03
Word Ordering	0.07	-0.09	0.08	0.15**	0.19***	-0.03	-0.08	-0.14*	0.02
Malapropisms	0.16**	-0.12*	0.09	0.19***	0.15**	-0.061	-0.12*	-0.12*	0.06

4. Discussion

This study suggests that the negative effects of prenatal cocaine exposure on language skills continue to be evident at 10 years of age, a time when children are acquiring critical reading and writing skills necessary for success in school. Our findings are consistent with other reports that indicate that prenatal cocaine exposure continues to place children at risk for mild language deficits into preadolescence, a time when cognitive and linguistic demands increase academically and socially [5]. These effects are subtle and may impact specific cognitive skills rather than overall language abilities. For example, while we found more global cognitive deficits in our cohort at 2 years [40], by 4 years of age deficits of children with PCE were specific to visual-spatial skills, arithmetic skills, and general knowledge [43] and by 9 years perceptual organizational skills were differentially affected [44]. Our results suggest that children with PCE may be at risk for deficits in specific language skills at preadolescence due to a combination of biological maturation and increasing academic and social demands.

4.1. Effects of cocaine on spoken language

Two subtests, Sentence Combining and Malapropisms, of the TOLD-P:I were significantly affected by prenatal cocaine exposure even after adjustment for multiple covariates (i.e. the HOME, current caregiver's vocabulary, and GSI) were made. The Sentence Combining subtest measures of syntactic ability as the child is asked to create one compound or complex sentence from two or more simple sentences that are presented auditorily. This subtest requires the child to use compound subjects, objects, verbs and verb phrases, skills that are essential to academic and social success in middle school and beyond. The Malapropisms subtest is a measure of semantic knowledge as the child is required to identify words that sound like the appropriate words but have absurd meanings in a particular context. These stimuli are also presented auditorily, thus playing a central role on accurate listening skills. Semantic deficits have been reported in other studies of children with PCE. Delaney-Black et al. [12] classified children into low language group based on semantic measures (type-token ratios and word types) and found that children with PCE were more likely to fall into the low language group than NCE children. They suggest the possibility that a language threshold may exist for successful academic achievement with children with PCE more often falling below this threshold. Studies of reading comprehension have demonstrated that both spoken syntax and semantic skills are the best predictors of reading

comprehension for kindergarten and first grade children [10,28]. Vocabulary in particular has been related to single word reading with children who have larger vocabularies better able to identify written words [49]. At 10 years of age, children with PCE may be at risk for reading comprehension deficits due to poor syntax and semantic skills.

4.2. Effects of cocaine on phonological processing

An effect for cocaine exposure on the Phonological Awareness subtest of the CTOPP also remained significant after controlling for covariates. Phonological awareness is an auditory processing skill that has been associated with decoding printed words and the acquisition of fluent reading skills [11,24,35,37,47]. Phonological Awareness is a metalinguistic skill that includes awareness that spoken units of speech are comprised of smaller units such as syllables, individual phonemes and sounds. In particular, the Elision subtest of the CTOPP which requires the child to delete sounds and syllables of words has been associated with both skills in reading decoding and reading comprehension [28]. In the current study, a significant cocaine effect was observed for the Elision subtest of the CTOPP, with children with PCE performing more poorly than NCE children. Proficient early reading skills are dependent on the child's ability to rapidly decode or sound out words. Children with PCE may be less efficient decoders and therefore at risk for reading difficulties due to phonological processing problems. Prenatal exposure to cigarettes and marijuana has been related to poor language and reading outcomes in 9–12 year-old children [17], with these authors suggesting that altered auditory functioning may be an important cause to consider. In our early report of this cohort, we found auditory comprehension deficits in children with PCE [40]. It seems likely that the finding of poor phonological awareness skills at 10 years of age may be related to our earlier finding of auditory deficits in this sample. Thus, prenatal cocaine exposure impacts both higher level language abilities and phonological awareness skills that are essential for the development of literacy skills and academic success.

4.3. Cocaine by gender interaction

Cocaine by gender interaction was observed for girls in this sample. Girls with PCE performed more poorly than girls without prenatal cocaine exposure on language measures including the Phonological Awareness subscale of the CTOPP. This finding is consistent with Beeghly et al.'s [4] finding of lower expressive and total language scores for females with PCE. A longitudinal study of children with PCE at 4, 6, and 9 years demonstrated a cocaine by gender interaction with boys with PCE consistently demonstrating lower IQs than girls with PCE across all ages [6]. Boys with PCE demonstrated lower scores on the Visual/Abstract reasoning scale. Thus, while it appears that there are gender-specific effects of prenatal cocaine exposure, these effects may differ by the specific cognitive skill assessed (i.e. Phonological Awareness, overall language skills or other cognitive skills).

4.4. Environmental variables and language skills

Environmental variables continued to impact language skills at 10 years. Home environment, current caregiver vocabulary and psychological symptoms are significant predictors of language development among 10-year-old children both with PCE and without exposure. The current caregiver's vocabulary score and the HOME score both were related to language performance, underscoring the environmental modifiability of language. Reports of delays in syntax (i.e. the Sentence Combining subtest of the TOLD-I:3) and semantics (i.e. the Malapropism Subtest of the TOLD-I:3) in children exposed to cocaine may relate to the caregiver's vocabulary, as well as the cocaine exposure itself. We previously reported the relationship of caregiver's vocabulary to child's language at 4 and 6 years of age [26]. The impact

of the caregiver's vocabulary and the caregiver's psychological distress appears to continue into the school years in our sample.

Environmental lead exposure measured during early childhood was also related to language deficits at 10 years of age. Significant effects of lead exposure were observed on the Phonological Awareness and Elision subtests of the CTOPP and the Sentence Combining, Picture vocabulary, and Grammatical Comprehension subtest scores of the TOLD-I:3. Early childhood lead exposure has been noted to have a significant impact on the brain reorganization associated with language functions [50].

4.5. Children with PCE in adoptive/foster care

In our prior studies the foster/adoptive caregiver's vocabulary, depression, and HOME scores contributed to the adoptive-care effect on language at 4 years of age [27] and cognitive and achievement outcomes at 9 years of age [44]. The protective effect of adoptive/foster care was also observed on language skills at 10 years of age. Cocaine exposed children in family care had poorer language scores than children in adoptive/foster care.

5. Conclusions

The findings from this study support the notion that language outcomes at 10 years of age are the result of prenatal cocaine exposure and environmental conditions. Future studies should attempt to identify specific linguistic deficits in semantic, syntactic, phonological and pragmatic skills that are associated with cocaine exposure and determine how these deficits impact literacy development and social skills. Pediatricians and educators should be aware of the risks of prenatal cocaine and early childhood lead exposure may extend into the school age years and continue to monitor children appropriately.

5.1. Limitations of the current study

While the strengths of the current study include the use of a prospective design, detailed postnatal maternal interviews and biological markers (i.e., meconium and urine) to determine cocaine status, an excellent retention rate, examiners blinded to cocaine status, and the assessment of specific language skills, there are several weaknesses of the study that should be noted. First, the study sample was limited to African-American children in disadvantaged neighborhoods. The cumulative effects of such an impoverished environment on language are not known and warrant further study. Some children with PCE were exposed to multiple drugs, including marijuana, alcohol, and nicotine, as well as environmental toxins. Also the standardized tests employed in this study did not tap all components of language and may not have been sensitive to subtle deficits in language and phonological processing. Cocaine effects may be specific to other domains of language that were not assessed. Finally, the age at assessment, 10 years, may not have captured the full impact of cocaine exposure on language skills as these skills continue to develop into adolescence. Additional follow-up at adolescence is warranted employing measures that tap specific metalinguistic skills.

Conflict of interest statement

Nothing declared.

Acknowledgements

This work is supported by Grant R01-DA07957 from the National Institute on Drug Abuse. Thanks are extended to Terri Lotz-Ganley for manuscript preparation; Laurie Ellison, Nicole Nall, and Addie Lang for research and data analytic assistance, and the Cuyahoga County Department of Children and Family Services.

References

- [1] M. Angelilli, H. Fischer, V. Delaney-Black, M. Rubenstein, J. Ager, R.J. Sokol, History of in utero cocaine exposure in language-delayed children, *Clinical Pediatrics* 33 (1994) 514–516.
- [2] E.S. Bandstra, C.E. Morrow, A.L. Vogel, R.C. Fifer, A.Y. Ofir, A.T. Dausa, L. Xue, J.C. Anthony, Longitudinal influence of prenatal cocaine exposure on child language functioning, *Neurotoxicology and Teratology* 24 (2002) 297–308.
- [3] M. Beeghly, G. Brilliant, N. Dyer, H. Park, E.Z. Tronick, R. Rose-Jacobs, Language development of prenatally drug exposed and nonexposed toddlers at high social risk, *International Conference on Infant Studies*, Providence R.I., 1996.
- [4] M. Beeghly, B. Martin, R. Rose-Jacobs, H. Cabral, T. Heeren, M. Augustyn, D. Bellinger, D.A. Frank, Prenatal cocaine exposure and children's language functioning at 6 and 9.5 years: moderating effects of child age, birthweight, and gender, *Journal of Pediatric Psychology* 31 (2006) 98–115.
- [5] D.S. Bennett, M. Bendersky, M. Lewis, Children's intellectual and emotional-behavioral adjustment at 4 years as a function of cocaine exposure, maternal characteristics, and environmental risks, *Developmental Psychology* 38 (2002) 648–658.
- [6] D.S. Bennett, M. Bendersky, M. Lewis, Children's cognitive ability from 4 to 9 years old as a function of prenatal cocaine exposure, environmental risk, and maternal verbal intelligence, *Developmental Psychology* 44 (2008) 919–928.
- [7] L.M. Bland-Stewart, H.N. Seymour, M. Beeghly, D.A. Frank, Semantic development of African-American children prenatally exposed to cocaine, *Seminars in Speech and Language* 19 (1998) 167–187.
- [8] R.H. Bradley, B.M. Caldwell, S.L. Rock, C.T. Ramey, Home environment and cognitive development in the first 3 years of life: a collaborative study involving 6 sites and 3 ethnic groups in North America, *Developmental Psychology* 25 (1989) 217–235.
- [9] B. Cadwell, R. Bradley, Home observation for measurement of the environment, Editoin Edition, University of Arkansas Press, Little Rock, AK, 1984.
- [10] H.W. Catts, The relationship between speech–language impairments and reading disabilities, *Journal of Speech and Hearing Research* 36 (1993) 948–958.
- [11] H.W. Catts, M.E. Fey, X. Zhang, J.B. Tomblin, Language basis of reading and reading disabilities: evidence from a longitudinal investigation, *Scientific Studies of Reading* 3 (1999) 331–362.
- [12] V. Delaney-Black, C. Covington, T. Templin, T. Kershaw, B. Nordstrom-Klee, J. Ager, N. Clark, A. Surendran, S. Martier, R.J. Sokol, Expressive language development of children exposed to cocaine prenatally: literature review and report of a prospective cohort study, *Journal of Communication Disorders* 33 (2000) 463–481.
- [13] L. Derogatis, The Brief Symptom Inventory: Administration, scoring, and procedures manual, Edition, Editoin Edition, Clinical Psychometric Research, Inc., Baltimore, MD, 1992.
- [14] L.M. Dunn, L.M. Dunn, G.J. Robertson, J.L. Eisenberg, Peabody Picture Vocabulary Test-Revised, Editoin Edition, American Guidance Service, Circle Pines, MN, 1981.
- [15] K.A. Epsy, P. Kaufmann, M. Glisky, Neuropsychologic function in toddlers exposed to cocaine in utero: a preliminary study, *Developmental Neuropsychology* 15 (1999) 447–460.
- [16] D.A. Frank, R. Rose-Jacobs, M. Beeghly, M. Wilbur, D. Bellinger, H. Cabral, Level of pre-natal cocaine exposure and 48-month IQ: importance of preschool enrichment, *Neurotoxicology and Teratology* 27 (2005) 15–28.
- [17] P.A. Fried, B. Watkinson, L.S. Siegel, Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana, *Neurotoxicology and Teratology* 19 (1997) 171–183.
- [18] D.D. Hammill, P.L. Newcomer, Test of language development-3rd Edition, Intermediate, Editoin Edition, Pro-Ed, Austin, TX, 1997.
- [19] C.J. Hobel, M.A. Hyvarinen, D.M. Okada, W. Oh, Prenatal and intrapartum high-risk screening. I. Prediction of the high-risk neonate, *American Journal of Obstetrics and Gynecology* 117 (1973) 1–9.
- [20] A.B. Hollingshead, Four factor index of social status, Unpublished manuscript, Department of Social Work, Yale University, New Haven, CT, 1975.
- [21] H. Hurt, L. Malmut, N.L. Betancourt, J.A. Brodsky, A. Giannetta, A prospective evaluation of early language development in children with in utero cocaine exposure in control subjects, *The Journal of Pediatrics* 130 (1997) 310–312.
- [22] J.L. Jacobson, S.W. Jacobson, Detecting the effects of prenatal drug exposure in socio-environmentally-deprived children, in: M. Lewis, M. Bendersky (Eds.), *Cocaine Mothers and Cocaine Babies: The Role of Toxins in Development*, Erlbaum, Hillsdale, NJ, 1995.
- [23] S.W. Jacobson, J.L. Jacobson, R.J. Sokol, S.S. Martier, L.M. Chiodo, New evidence for neurobehavioral effects of in utero cocaine exposure, *The Journal of Pediatrics* 129 (1996) 581–590.
- [24] L.M. Justice, R.P. Bowles, L.E. Skibbe, Measuring preschool attainment of print concept knowledge: a study of typical and at-risk 3 to 5-year-old children using item response theory, *Language, Speech, and Hearing Services in Schools* 37 (2006) 224–235.
- [25] H. Killbride, C. Castor, E. Hoffman, K.L. Fuger, Thirty-six-month outcome of prenatal cocaine exposure for term or near term infants: impact of early case management, *Journal of Developmental and Behavioral Pediatrics* 21 (2000) 19–26.
- [26] B.A. Lewis, H.L. Kirchner, E.J. Short, S. Minnes, P. Weishampel, S. Satayathum, L.T. Singer, Prenatal cocaine and tobacco effects on children's language trajectories, *Pediatrics* 120 (2007) e78–e85.
- [27] B.A. Lewis, L.T. Singer, E.J. Short, S. Minnes, R. Arendt, P. Weishampel, N. Klein, M.O. Min, Four-year language outcomes of children exposed to cocaine in utero, *Neurotoxicology and Teratology* 26 (2004) 617–627.
- [28] L.J. Lombardino, C.A. Riccio, G.W. Hynd, S.B. Pinheiro, Linguistic deficits in children with reading disabilities, *American Journal of Speech-Language Pathology* 6 (1997) 71–78.
- [29] C.L. Madison, J.A. Johnson, M. Seikel, L. Arnold, L. Schultheis, Comparative study of phonology of preschool children prenatally exposed to cocaine and multiple drugs and nonexposed children, *Journal of Communication Disorders* 31 (1998) 231–243.
- [30] M. Mentis, K. Lundgren, Effects of prenatal exposure to cocaine and associated risk factors on language development, *Journal of Speech and Hearing Research* 38 (1995) 1303–1318.
- [31] R.M. Mickey, S. Greenland, The impact of confounder selection criteria on effect estimation, *American Journal of Epidemiology* 129 (1989) 125–137.
- [32] S. Minnes, L.T. Singer, R. Arendt, S. Satayathum, Effects of prenatal cocaine/polydrug use on maternal–infant feeding interactions during the first year of life, *Infant Behavior & Development* 26 (2005) 194–200.
- [33] C.E. Morrow, E.S. Bandstra, J.C. Anthony, A.Y. Ofir, L. Xue, M.B. Reyes, Influence of prenatal cocaine exposure on early language development: longitudinal findings from four months to three years of age, *Journal of Behavioral Pediatrics* 24 (2003) 39–50.
- [34] C.E. Morrow, A.L. Vogel, J.C. Anthony, A.Y. Ofir, A.T. Dausa, E.S. Bandstra, Expressive and receptive language functioning in preschool children with prenatal cocaine exposure, *Journal of Pediatric Psychology* 29 (2004) 543–554.
- [35] L. Nathan, J. Stackhouse, N. Goulondris, M.J. Snowling, The development of early literacy skills among children with speech difficulties: a test of the “critical age” hypothesis, *Journal of Speech, Language, and Hearing Research* 47 (2004) 337–361.
- [36] J.S. Noland, L.T. Singer, E.J. Short, S. Minnes, R.E. Arendt, H.L. Kirchner, C. Bearer, Prenatal drug exposure and selective attention in preschoolers, *Neurotoxicology and Teratology* 27 (2005) 429–438.
- [37] H.S. Scarborough, Developmental relationships between language and reading: reconciling a beautiful hypothesis with some ugly facts, in: H.W. Catts, A.G. Kamhi (Eds.), *The Connections Between Language and Reading Disabilities*, Erlbaum, Mahwah, NJ, 2005, pp. 3–24.
- [38] R. Seifer, L.L. LaGasse, B. Lester, S.S. Bauer C.R., H.S. Bada, L.L. Wright, V.L. Smeriglio, J. Liu, Attachment status in children prenatally exposed to cocaine and other substances, *Child Development* 75 (2004) 850–868.
- [39] L. Singer, R. Arendt, S. Minnes, K. Farkas, A. Salvator, Neurobehavioral outcomes of cocaine-exposed infants, *Neurotoxicology and Teratology* 22 (2000) 653–666.
- [40] L.T. Singer, R. Arendt, S. Minnes, K. Farkas, A. Salvator, H.L. Kirchner, R. Kliegman, Cognitive and motor outcomes of cocaine-exposed infants, *JAMA, the Journal of the American Medical Association* 287 (2002) 1952–1960.
- [41] L. Singer, R. Arendt, S. Minnes, A. Salvator, A.C. Siegel, B.A. Lewis, Developing language skills of cocaine-exposed infants, *Pediatrics* 107 (2001) 1057–1064.
- [42] L. Singer, L.J. Eisengart, S. Minnes, J. Noland, A. Jey, C. Lane, M.O. Min, Prenatal cocaine exposure and infant cognition, *Infant Behavior & Development* 28 (2005) 431–444.
- [43] L.T. Singer, S. Minnes, E. Short, R. Arendt, K. Farkas, B. Lewis, N. Klein, S. Russ, M.O. Min, H.L. Kirchner, Cognitive outcomes of preschool children with prenatal cocaine exposure, *JAMA, the Journal of the American Medical Association* 29 (2004) 2448–2456.
- [44] L.T. Singer, S. Nelson, E. Short, M.O. Min, B. Lewis, S. Russ, S. Minnes, Prenatal cocaine exposure: drug and environmental effects at 9 years, *The Journal of Pediatrics* 153 (2008) 105–111.
- [45] S.B. Uhlhorn, D.S. Messinger, C.R. Bauer, Cocaine exposure and mother–toddler play, *Infant Behavior & Development* 28 (2005) 62–73.
- [46] R. Wagner, J. Torgesen, C. Rashotte, The comprehensive test of phonological processing, Editoin Edition, Pro-Ed, Inc., Austin, TX, 1999.
- [47] P.E. Webster, A.S. Plante, L.M. Couvillion, Phonological impairment and prereading: update on a longitudinal study, *Journal of Learning Disabilities* 30 (1997) 365–375.
- [48] D. Wechsler, Weschler Adult Intelligence Scale-Revised, Edition, Editoin Edition, The Psychological Corporation, San Antonio, TX, 1989.
- [49] J.C. Wise, R.A. Sevcik, R.D. Morris, M.W. Lovett, M. Wolf, The relationship among receptive and expressive vocabulary, listening comprehension, pre-reading skills, word identification skills, and reading comprehension by children with reading disabilities, *Journal of Speech, Language, and Hearing Research* 50 (2007) 1093–1109.
- [50] W. Yuan, S.K. Holland, K.M. Cecil, K.N. Dietrich, S.D. Wessel, M. Altaye, R.W. Hornung, M.D. Ris, J.C. Egelhoff, B.P. Lanphear, The impact of early childhood lead exposure on brain organization: a functional magnetic resonance imaging study of language function, *Pediatrics* 118 (2006) 971–977.