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Level of Intrauterine Cocaine Exposure and Neuropsychological Test Scores in Preadolescence: Subtle Effects on Auditory Attention and Narrative Memory

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Abstract

Neuropsychological processes such as attention and memory contribute to children's higher-level cognitive and language functioning and predict academic achievement. The goal of this analysis

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was to evaluate whether level of intrauterine cocaine exposure (IUCE) alters multiple aspects of preadolescents' neuropsychological functioning assessed using a single age-referenced instrument, the *NEPSY: A Developmental Neuropsychological Assessment* (NEPSY) [71], after controlling for relevant covariates. Participants included 137 term 9.5-year-old children from low-income urban backgrounds (51% male, 90% African American/Caribbean) from an ongoing prospective longitudinal study. Level of IUCE was assessed in the newborn period using infant meconium and maternal report. 52% of the children had IUCE (65% with lighter IUCE, and 35% with heavier IUCE), and 48% were unexposed. Infants with Fetal Alcohol Syndrome, HIV seropositivity, or intrauterine exposure to illicit substances other than cocaine and marijuana were excluded. At the 9.5-year follow-up visit, trained examiners masked to IUCE and background variables evaluated children's neuropsychological functioning using the NEPSY. The association between level of IUCE and NEPSY outcomes was evaluated in a series of linear regressions controlling for intrauterine exposure to other substances and relevant child, caregiver, and demographic variables. Results indicated that level of IUCE was associated with lower scores on the *Auditory Attention* and *Narrative Memory* tasks, both of which require auditory information processing and sustained attention for successful performance. However, results did not follow the expected ordinal, dose-dependent pattern. Children's neuropsychological test scores were also altered by a variety of other biological and psychosocial factors.

Keywords

Intrauterine cocaine exposure; preadolescents; neuropsychological functioning; auditory attention; narrative memory; *NEPSY-A Developmental Neuropsychological Assessment*

1. Introduction

In both animal and human studies, intrauterine cocaine exposure (IUCE) has been shown to alter monoaminergic neurotransmitter systems during gestation [20,90], which may influence developing mechanisms underlying the regulation of attention and affect, executive functions, and motor control [77,82,90]. These alterations are concerning because they have potential implications for the development of higher cognitive processes, such as language, memory, and learning [4,9,38,89,106], as well as academic achievement [24,112].

Although the effects of IUCE on fetal growth and newborn neurobehavior are fairly robust [44,56,78,136], reports of IUCE effects on neuropsychological functioning beyond early childhood are not consistent. Many large well-controlled studies find no significant effects of IUCE on general intelligence or academic achievement at school age [3,63,98,109,113,137]. In one study, IUCE was associated with poorer performance on the Perceptual Reasoning composite from the *Wechsler Intelligence Scale for Children* (WISC-IV)[138] but not the Verbal Comprehension, Working Memory, or Processing Speed composites, or scores on a standardized achievement test [124].

When significant IUCE effects on specific neuropsychological functions are reported in this literature, results often vary from sample to sample and tend to be subtle rather than global or devastating [3,76,115]. Moreover, the magnitude of IUCE effects is often attenuated when the effects of biological and environmental risk and protective factors on

neuropsychological functioning are covaried [3,7,37,87]. In recent reviews, the most consistent IUCE effects on children's neuropsychological functioning after covariate control have been reported for language, attention, memory, and associated executive control processes (e.g., arousal, impulsivity, inhibition) [3,23].

1.1. IUCE and Neuropsychological Functioning

1.1.1. Language—A growing body of results from several large well-designed, covariate-controlled prospective studies suggests that IUCE may be linked to mild but persistent language delays in preschool, school-aged, and early adolescent children, although specific findings vary [10,12,13,79,80]. Bandstra and colleagues [10] evaluated the developing language skills of a large urban sample of cocaine-exposed and unexposed children at 3, 5, and 12 years of age using an age-appropriate version of a single standardized assessment, the *Clinical Evaluation of Language Fundamentals* (CELF) [120]. Results of latent growth curve modeling revealed that a dichotomous measure of IUCE (exposed/unexposed) was associated with lower expressive and total language scores after controlling for prenatal exposure to tobacco, alcohol, and marijuana, and other medical and socio-demographic covariates. In a second analysis, a latent variable reflecting level of IUCE had a linear, dose-dependent relationship with receptive, expressive, and total language scores, controlling for child age, sex, and other prenatal exposures. However, the associations for receptive and expressive language scores were attenuated when other covariates were added to the model.

Contrasting findings were reported in other covariate-controlled prospective studies of children with and without IUCE. In a longitudinal analysis of children's standardized receptive, expressive, and total language scores during the first six years of life, Lewis and colleagues [79] reported a stable negative effect of IUCE on all language measures; however, prenatal tobacco exposure and environmental measures also accounted for significant, unique variance in language outcomes. In a follow-up of this cohort at age 10, Lewis et al.[80] found that IUCE was associated with mild compromise on specific rather than general measures of language, including syntax, semantics, and phonological processing.

In a longitudinal analysis of language data collected in the present cohort at ages 6 and 9.5 years, Beeghly et al.[13] reported no significant main effects of IUCE on standardized language scores; however, significant interactions of IUCE with child age, sex, and birth weight on language outcomes were found. Specifically, children with IUCE had lower receptive language scores than unexposed children at age 6, but not at age 9.5 years, and girls with IUCE had lower expressive and total language scores at both ages, compared to girls without IUCE and boys regardless of exposure status. Moreover, children with IUCE with a lower birth weight had lower expressive language scores than children with IUCE with a higher birth weight.

1.1.2. Attention and Associated Executive Control Processes—Recent reviews of IUCE studies with school-aged and adolescent children suggest that IUCE is linked to subtle alterations in attention and associated executive control processes, such as arousal, impulsivity, task persistence, and response inhibition, as assessed using performance-based

neuropsychological measures [3,23]. These findings are concerning because these regulatory processes underlie children's ability to engage in independent goal-directed behavior and complex learning tasks [81], which are increasingly required in higher education. Deficits in attention and other executive functions may undermine children's academic performance and social emotional competence in the elementary school years and beyond [125].

To date, most studies on the effects of IUCE on attentional processes have evaluated visual attention and related executive functions. In several analyses based on data collected in a large covariate-controlled prospective study, children with IUCE had significantly lower scores on measures of sustained visual attention assessed at ages 3, 5, and 7 years, as well as greater variability in performance, slower response time, and more omission (but not commission) errors at age seven [1,11]. A similar IUCE-related increase in omission errors on a continuous performance task was reported after covariate control in two independent cohorts; one at age 6 [109] and the other at age 7 [2]. In contrast, in two other studies, IUCE was associated with higher rate of commission (but not omission) errors on a continuous performance tasks at age 4 [101] and on a distractibility task with high performance demands at age 10 [116].

Findings in this literature are not entirely consistent. In one prospective longitudinal study, no direct IUCE effects on visual attention and other dimensions of executive functioning were observed ages 5 or 7 [40]. However, IUCE was indirectly associated with attention and other dimensions of executive functioning via its effect on head circumference at birth. The quality of children's caregiving environment and caregivers' functioning also accounted for a significant proportion of the variance.

Although understudied, there is increasing evidence suggesting that IUCE may also alter auditory attention processes, which may contribute to the language impairments reported for this population. In the animal literature, IUCE has been shown to accelerate aspects of the cochlear sensorineural maturation process, which may desynchronize development of the auditory pathway and lead to auditory dysfunction, and may in turn be associated with altered auditory brainstem response identified in experimental animals postnatally [134]. Similarly, using a protocol designed to capture primary features of human recreational cocaine usage, Mactutus et al. showed that IUCE in rats was associated with persistent alterations in auditory information processing and with dysfunction in the central noradrenergic circuitry modulating these responses [86]. In human studies, IUCE has been linked to alterations in newborns' auditory brainstem responses [131] and to slowed auditory information processing during an habituation paradigm [108], each of which could interfere with language development and general learning in later childhood. Beyond the newborn period, IUCE has been linked to deficits in auditory processing at one year of age [122], altered auditory threshold at age 7 [27], and altered speech processing ability among adolescents as assessed using event-related potentials [74].

1.1.3. Memory—Recent reviews suggest that IUCE is associated to alterations in verbal and non-verbal memory [3,23]. In animal research, IUCE is associated with non-spatial short-term working memory deficits in juvenile and adult rats [97]. In studies of human infants and young children, heavier IUCE predicts poorer visual recognition memory and

information processing as assessed using the Fagan Test of Infant Intelligence [65], and working memory deficits, particularly under conditions of stress [82]. Beyond early childhood, findings regarding the effects of IUCE on memory functions in well-controlled prospective follow-up studies are mixed; see [3,23] for reviews. In one study, no significant IUCE effects on working memory and other neuropsychological functions were observed at school age [62]. In a relatively small study, IUCE was associated with slower processing speed on a novel visuospatial working memory task [119]. In other studies, IUCE and other drug exposures are associated with lower scores on memory and other neuropsychological tests in adolescence [19,111]. In covariate-controlled analyses with school-aged children in the present cohort, children with heavier IUCE, compared to children with lighter IUCE or no IUCE, exhibited mild compromise on the Interference score from the Stroop Color-Word test, a measure of verbal inhibitory control requiring short-term working memory; however, IUCE effects on other standard tests were not observed [115].

1.2. Effects of Other Prenatal Exposures on Neuropsychological Functioning

Without appropriate control for polydrug exposure, it is difficult to make firm conclusions about specific IUCE effects on neuropsychological functioning because IUCE often co-occurs with intrauterine exposure to tobacco, alcohol, and marijuana [75,77,96], and each substance has been shown to alter children's neuropsychological functioning in multiple domains [60,79,96,124], including language, attention, memory, and associated executive control processes [32,110]. Willford et al.[141] found that prenatal exposure to tobacco, alcohol, and marijuana each accounted for significant, unique variance in processing speed and the inter-hemispheric transfer of information.

As is the case for IUCE, intrauterine exposure to tobacco is robustly associated with impaired fetal growth, and some studies suggest that it is also linked to increased activity and poor emotion regulation in early childhood, lower IQ scores throughout childhood [51,58,96], and heightened risk for attention problems from the preschool period through adolescence [32,101]. Kable et al. [66] used fast auditory brainstem responses to assess whether prenatal tobacco exposure was associated with differences in infants' sensory processing of auditory information. They found that infants who had been exposed to tobacco prenatally had longer-latency auditory brainstem responses. However, perinatal complications and prenatal alcohol exposure also contributed to this effect. In a study of adolescents, intrauterine tobacco exposure was linked to gender-specific deficits in both visual and auditory attention processes, as well as to concomitant changes in the efficiency of neurocircuitry supporting auditory attention processes [64]. In animal research, chronic neonatal nicotine exposure was associated to alterations in auditory learning in adulthood [83].

Similar results are reported for older children with intrauterine tobacco but not cocaine exposure. In a Canadian sample of 6- to 11-year-old mostly middle class children, intrauterine tobacco exposure was linearly, negatively associated with poorer performance on a central auditory processing task (Screening Test for Auditory Processing Disorders, SCAN) [67], controlling for passive environmental tobacco exposure and other covariates [91].

Intrauterine exposures to alcohol and marijuana are also linked to a variety of altered neuropsychological processes, including memory [32,50,51]. In a longitudinal prospective study, intrauterine exposure to alcohol was associated with impaired performance on a standardized memory battery at age ten, in the absence of Fetal Alcohol Spectrum Disorder [110]. In other work, intrauterine alcohol exposure had persistent and specific negative effects on memory performance in adulthood, problems that may stem from less efficient encoding of information across both verbal and nonverbal modalities [31]. In turn, intrauterine exposure to marijuana is linked to problems in sustained attention at preschool-age [101], greater impulsivity on a continuous performance task at age ten (Richardson et al, 2002) and persistently poor performance across childhood on executive function tasks tapping higher-order cognitive functioning, including memory, planning, and attention [50,52].

1.3. Effects of Other Biologic and Social Factors

In both the IUCE and general child development literatures, a broad array of other risk factors such as poverty, environmental lead exposure, and violence exposure are robustly associated with children's impaired neuropsychological functioning, including attention and memory, and as well as to general indices of cognitive and language performance (see, e.g., [26,41,80,124]). Similarly, protective factors such as being raised by caregivers with higher education and less psychological distress, growing up in a higher quality home environment, receiving early interventions, and participating in high quality preschool programs are linked to more optimal child neuropsychological and general cognitive and language outcomes [13,21,48,98,124].

Moreover, child sex is linked to neuropsychological functioning at school age, with girls tending to perform better on language and memory tests, and boys tending to perform better on visuospatial tests [129]. Child sex also moderates IUCE effects on children's cognitive functioning at school age, although specific effects vary depending on the cohort and specific outcome in question (e.g.,[13,17]). As is the case for intrauterine polydrug exposure, biologic and social factors such as these may act as confounding factors in behavioral teratology research and need to be evaluated as potential control variables [13,28,41,69,95,124,135].

1.4. Objectives of the Present Study

The primary goal of the current analysis was to evaluate whether level of IUCE is associated with multiple dimensions of neuropsychological functioning at preadolescence assessed using a single age-referenced neuropsychological assessment, the NEPSY-A Developmental Neuropsychological Assessment (NEPSY) [71], controlling for relevant covariates. The NEPSY was selected because it provides a comprehensive set of neuropsychological measures that were co-normed on the same national standardization sample. All dimensions assessed by the NEPSY were evaluated in the present study, given increasing evidence for neurological intennections between brain regions that support multiple neurocognitive functions [14,15,35]. However, we were particularly interested in IUCE effects on language, attention, and memory, as these neuropsychological domains are most often linked to IUCE in the behavioral teratology literature beyond early childhood [3,23,109].

2. Methods

2.1. Participants

Analyses were based on children's neuropsychological test scores derived from the NEPSY [71], which were collected at the 9.5-year visit in an ongoing prospective longitudinal study of the effects of IUCE on growth and development from birth through adolescence. Level of IUCE, prenatal exposure to other substances (tobacco, marijuana, and alcohol) and other child, caregiver, and demographic variables were available for our use from the data set of the original study. All study children were born at Boston City Hospital (now Boston Medical Center) and were from low-income urban backgrounds. The Institutional Review Board of Boston University Medical Campus and Boston City Hospital/Boston Medical Center approved the study. All birth mothers provided written informed consent at intake, as did all of the child's current caregivers (birth mothers, kinship caregivers, or nonkin foster/adoptive caregivers) at each follow-up visit. Child participants provided written assent beginning at the 8.5-year follow-up visit. All participants were protected by a certificate of confidentiality from the federal government which shielded research personnel from being compelled to release study records under subpoena.

2.2. Recruitment and Inclusion Criteria

Procedures regarding sample selection and recruitment have been reported in detail elsewhere [46,136]. Eligible infant-caregiver dyads were recruited in the neonatal period (intake) on a daily basis from the postpartum floor of Boston City Hospital between October 1990 and March 1993. Infants were eligible for recruitment if they were born at or near term (≥ 36 gestational weeks) and were healthy at the time of delivery, with no obvious major congenital malformations, no requirement for neonatal intensive care, no history of HIV seropositivity noted in infants' or mothers' medical records, and no diagnosis of Fetal Alcohol Syndrome in the neonatal record. Eligible infants also had no evidence of prenatal exposure to illegal opiates, methadone, amphetamines, phencyclidine, barbiturates, or hallucinogens, as documented either by neonatal or maternal urine toxic screen, meconium assay, or history in the medical record. Eligible mothers were at least 18 years old at the time of the infant's birth and fluent in English. These criteria were implemented to exclude mother-infant dyads with known major risk factors (e.g., premature birth, genetic anomalies, and young parenthood) that might confound any specific effects of IUCE on children's outcomes. Mothers were required to be fluent in English because the neuropsychological measures planned for this cohort at older ages were not standardized for non-English speakers.

2.3. Classification of IUCE

As reported previously [13,46,136], IUCE status was determined at intake using a combination of biological markers and maternal self-report. At least one biological assay (maternal or infant urine, or infant meconium) was obtained for each recruited dyad. Urine samples were analyzed for benzoylecognine, opiates, amphetamines, benzodiazepines, and cannabinoids by radioimmunoassay using commercial kits (Abuscreen RIA, Roche Diagnostics Systems, Inc., Montclair, NJ). Meconium specimens were also collected for the majority of enrolled infants (86%) for analysis by radioimmunoassay for the presence of

benzoylecognine, opiates, amphetamines, benzodiazepines, and cannabinoids, using a modification of Ostrea's method [103,104]. In addition, mothers were interviewed at intake (immediately postpartum) by research staff about their pregnancy and lifetime use of cigarettes, alcohol, and illicit drugs using an adaptation of the fifth edition of the Addiction Severity Index (ASI)[92]. Infants were classified as having IUCE if mothers' or newborns' urine or meconium was positive for cocaine metabolites or if mothers reported using cocaine during pregnancy. Conversely, infants were classified as unexposed to cocaine if their or their mothers' bioassays were negative for cocaine *and* if their mothers denied using cocaine or illicit drugs other than marijuana during pregnancy, *and* if no metabolites of illicit drugs other than marijuana were found on bioassays.

On the basis of combined information derived from the meconium assays and maternal self-report, infants with IUCE were further classified at birth as having either heavier or lighter IUCE. A classification system based on both meconium assay and maternal self-report was used for this purpose because 13.9% in the original sample at intake (13.86% in the present sample) had no meconium assay. “Heavier” exposure was defined *a priori* as the top quartile of days of maternal self-reported cocaine use during the entire pregnancy *and/or* the top quartile of concentration for cocaine metabolites in the infant's meconium. The average number of days of maternal self-reported cocaine use during pregnancy in the present sample was 20.4 days (20.6 in the original sample), with a range from 0 to 264 days. Mothers reporting 61 or more days of cocaine use during pregnancy fell into the top quartile and were considered “heavier” users. The average meconium concentration was 1143 *ng* of benzoylecognine per gram of meconium (range = 0–17,950 *ng*). Infants with more than 3314 *ng* of benzoylecognine per gram of meconium were in the top quartile and were classified into the “heavier” IUCE group. All other IUCE was classified as “lighter”.

Notably, mothers whose self-reported cocaine use during pregnancy fell in the top quartile were classified as heavier users, even if the benzoylecognine level in their infant's meconium fell below the top quartile, or if their infant's meconium assay was missing. This procedure was used because not all infants with IUCE have positive meconium assays [75] and because women are more likely to underreport than over-report illicit substance use during pregnancy [103].

Our ordinal IUCE classification scheme is similar to those used by other investigators of prenatal substance exposure [6,65,123]. Findings from prior analyses in this cohort indicated that IUCE defined this way was significantly related in a linear dose-dependent manner to lower birth weight *z*-scores adjusted for gestational age and sex [45], less optimal patterns of newborn neurobehavior [136], and neonatal ultrasound findings [46]. This ordinal IUCE classification of the sample (unexposed, lighter exposed, heavier exposed), which was established at birth, was used as the primary predictor of NEPSY outcomes in the current analysis.

2.4. Follow-Up Procedures

Following recruitment, caregiver-child dyads were evaluated prospectively at successive time points at a large, urban medical center in the northeastern United States. At each visit, the child's developmental and social emotional functioning was evaluated by trained

examiners masked to children's IUCE status and background variables in a child-friendly observational testing room. The child's current caregiver was interviewed in a separate room by a different researcher regarding demographics, recent substance use, caregiver and child psychosocial adaptation and exposure to violence, the family environment, and the child's involvement with the father. At each protocol point, the caregiver was also asked to provide a urine sample to evaluate current drug use.

2.5. Procedures at the 9.5-Year Visit: Neuropsychological Assessment

At the 9.5-year visit, trained examiners masked to IUCE status, developmental history, and family background evaluated multiple aspects of children's neuropsychological functioning using a single age-referenced instrument, the NEPSY-A Developmental Neuropsychological Assessment (NEPSY) [71]. Designed for children aged three to 12 years, the NEPSY is a comprehensive developmental neuropsychological assessment grounded in Luria's theory of integrated brain functioning [84,85] and extant traditions in neuropsychological assessment [68]. The NEPSY was standardized on a geographically, socioeconomically, and racially representative national sample of 1,000 male and female children. The 5-12 year version of the NEPSY was used in this study, which yields standard scores (population M = 100, SD = 15) for five different core domains of neuropsychological functioning *(Attention/Executive Functions, Language, Sensorimotor, Visuospatial, and Memory & Learning)* as well as scaled scores (population M=10, SD=3) for specific subtests associated with each core domain. Supplemental scales are described using raw scores.

Prior studies using the NEPSY in both typical and atypical child samples indicate that it has adequate psychometric properties, including discriminant and predictive validity [5,68,105]. In multiple studies, NEPSY scores are developmentally sensitive [70] and have been shown to significantly discriminate among at-risk, clinical, and typically developing groups of children, including children with neurological problems, survivors of extremely low birth weight, children with attention deficit disorders and other academic concerns, and children with a history of physical abuse and neglect [68,102,118].

The Attention/Executive Functions core domain evaluates a comprehensive set of attentional skills and executive functions, including selective and sustained visual and auditory attention, response set, nonverbal problem solving, figural fluency, inhibition, self-monitoring, and self-regulation [5,71]. In addition to the core domain score, three subtests from this core domain were evaluated in this study: *Tower, Visual Attention, and Auditory Attention*.

Because auditory attention has been understudied in the IUCE literature, and given its relevance to language development in the cognitive neuroscience literature [9,130] and possible relevance to prior reports of IUCE-related deficits in language in this and other cohorts [2,13,23] (Beeghly et al.,), the *Auditory Attention* subtest was of particular interest in this study. This subtest consists of two successive tasks (*Attention Task* and *Response Set*). In each task, children are asked to listen to an audio-recording of different color names presented in 1-second intervals, and to perform requested actions following the presentation of each color name. The first (*Attention Task*) is a simple sustained auditory attention task, in which children are asked to place a colored chip into a box when they hear its

corresponding color named in the audio-recording. The second (*Response Set*) is more complex and requires children to shift set, inhibit the responses they had been performing in the first task, and implement new ones. For instance, when children hear the word “red”, they are now asked to put a yellow chip into the box instead of a red one. Scores in each task are based on both the speed and accuracy of response.

The *Language* core domain taps specific neuropsychological functions associated with language and related academic skills such as reading. In addition to the core domain score, four subtests from this core domain were evaluated in this study: *Speeded Naming*, *Phonological Processing*, and *Comprehension of Instructions*. Bandstra and colleagues used the NEPSY Language core domain to create the composite language score used in their longitudinal analyses from early to middle childhood and showed it was sensitive to effects of IUCE and other risk factors [12]. All three subscales comprising the *Language* core domain have the potential to inform IUCE-specific language differences noted in prior research in this and other cohorts.

The *Sensorimotor* core domain evaluates specific neuropsychological functions associated with the planning and execution of fine motor skills, including the production of repetitive finger and rhythmic hand movements, the imitation of hand positions, and the execution of precise, speeded pencil movements. In addition to the core domain score, three subtests from this core domain were evaluated in this study: *Fingertip Tapping*, *Imitating Hand Positions*, and *Visuomotor Precision*. Although understudied, some reports suggest that sensorimotor functions, such as imitation of body postures and hand movements, contribute to children's general cognitive and language development [88].

The *Visuospatial* core domain evaluates multiple aspects of visuospatial processing including judgments about line orientations, copying two-dimensional designs based on a model, and the use of a small map to locate targets on a larger map. In addition to the core domain score, two subtests from this core domain were evaluated in this study: *Arrows* and *Design Copying*.

The *Memory and Learning* core domain evaluates multiple aspects of memory relevant to learning and academic success, including immediate sentence recall, immediate and delayed memory for names and faces, and immediate and delayed memory for narratives. In addition to the core domain score, three subtests from this core domain were evaluated in this study: *Memory for Faces*, *Memory for Names*, and *Narrative Memory*. The *Narrative Memory* subscale was of particular interest in the current analysis because of its reliance on verbal working memory and the ability to sustain auditory attention, both of which are linked to language development in the general literature [36,38,106] and may contribute to the IUCE-related language delays reported in prior work in this and other cohorts [2,13,23,77] . In this task, the examiner reads a story to the child, and then asks the child to recite it from memory. Following the task, multiple-choice items tapping recognition memory are administered.

2.6. Potential Control Variables

Candidate demographic, maternal/caregiver, and child control variables were identified on theoretical grounds at the onset of the original study and assessed at intake and/or at each subsequent visit via medical record review, caregiver interviews, or direct child or caregiver assessments. These variables were chosen because they have been associated with IUCE and/or with children's neurodevelopmental outcomes in prior research with this cohort or in other studies [7,10,13,16,18,26,62,64,80]. The specific variables evaluated as potential covariates in the present study are listed in Tables 1 and 2 and are described briefly below.

2.6.1. Birth mother control variables—Birth mothers' race/ethnicity, age at the time of the child's birth, years of completed education, marital status, parity, immigrant status, and receipt of public assistance were assessed at intake. These socio-demographic variables were evaluated because they have been shown to discriminate between mothers who use cocaine during pregnancy and mothers who do not, e.g., [16], and because they are known predictors of children's neurodevelopmental outcomes, both in the broader literature [26,41,69,93,121] and in prior studies of prenatal substance exposure, including this cohort. [3,13,48,79,95,98,113,124].

Mothers' prenatal use of psychoactive substances other than cocaine (i.e., tobacco, alcohol, and marijuana) was assessed at intake because prior research indicates that mothers who use cocaine during pregnancy are very likely to use these other substances as well [6,16,44,75,123]. Moreover, each of these intrauterine exposures independently has been linked to compromises in neuropsychological functioning during childhood and adolescence [50,58,113,141]. Maternal self-report measures of alcohol and tobacco use during pregnancy were evaluated because, at the time the study was initiated, there was no established biologic marker for gestational alcohol exposure, and cotinine assays were prohibitively expensive. Prenatal tobacco use was assessed using the natural log of mothers' average daily number of cigarettes consumed during pregnancy. Prenatal alcohol use was evaluated using the natural log of mothers' average daily volume of alcohol during the last 30 days of pregnancy. A comparable variable assessing alcohol consumption during the entire pregnancy was also available, but the former measure was evaluated in the present analysis because it is less subject to recall bias. Of note, these two variables were highly correlated ($r = 0.77$) in this sample. Prenatal marijuana use was defined dichotomously as any intrauterine use, based on the positive results of urine assay, meconium assay, and/or maternal self-report.

2.6.2. Current caregiver control variables—Potential control variables relevant to the child's current caregiver were assessed using interviews and questionnaires administered at the 9.5-year visit. Demographic variables included current caregivers' highest level of completed education, marital status, employment status, receipt of public assistance, and family size (number of adults and children living in the household [3,7,16,26,135]. Caregivers' current substance use was measured using a combination of urine bioassay and self-report using questions adapted from the Addiction Severity Index [92]. Caregivers also reported on their current levels of psychological distress using the Brief Symptom Inventory (BSI) [34], a standardized self-report scale. Scoring the BSI provides a summary score of the severity of caregivers' general psychological symptomatology, the Global Severity Index

(GSI), which has been linked to maternal cocaine use during pregnancy and shown to alter the association between IUCE and children's outcomes in several longitudinal IUCE studies [13,79,80,124].

Given the well-documented negative effects of exposure to violence or victimization on caregivers' and children's psychosocial adaptation and children's developmental outcomes [8,13,23,69], caregivers reported on their own and their child's exposure to violence or victimization using the Exposure to Violence Inventory, EVI [8]. For analytic purposes in this study, a dichotomous variable reflecting the presence or absence of any child or caregiver exposure to violence or victimization during the past year was derived from the EVI.

2.6.3. Child control variables—Child variables shown in prior research to be associated with IUCE and/or neuropsychological functioning were also evaluated as potential covariates in the multivariate regressions. These included sex, [13,64] birth weight *z*-score (adjusted for gestational age and sex, based on norms calculated from data compiled by the National Center for Health Statistics for natality in the United States in 1991 [99], prior enrollment in a formal preschool program (e.g., Head Start) [48], any receipt of special education services or grade retention [113], current custody arrangements (birth mother, kinship caregiver, or nonkin foster/adoptive caregiver) and number of changes in caregiver since birth [22,47,117], and maximum whole blood lead values through age four [28,95]. Children's blood lead and hemoglobin values were obtained as part of the child's primary care visits and/or were abstracted from medical records during the preschool years.

Because caregivers may not have full knowledge of their preadolescent children's experiences, children also reported on their own exposure to violence and current depressive symptomatology at the 9.5-year visit. Exposure to violence was assessed using the Violence Exposure Scale-Revised (VEX-R) [42], a 21-item, 4-point Likert scale, cartoon-based measure assessing children's experience of witnessing and suffering violence, ranging from mild (yell, push, spank) to severe (threaten with a weapon, shoot, stab). Summed items yielded a total score (range=0-66).

Children's current depressive symptoms were evaluated as a potential covariate because a higher level of depressive symptomatology is linked to environmental stressors such as poverty and may undermine children's cognitive and academic functioning [29,133]. Children's self-report of depressive symptoms experienced during the past two weeks was evaluated using the 27-item Children's Depression Inventory (CDI) [72]. For each 3-point ordinal scale item, children selected the sentence most accurately describing their feelings during this time period (total score range=0-54).

In order to control for the possible confounding effect of children's general intelligence on specific aspects of neuropsychological functioning [12,80], children's prorated IQ was included as a control variable in the multivariate regressions for all NEPSY outcomes. Prorated IQ was evaluated using a short form of the Wechsler Intelligence Scale for Children (WISC-III) [139] at the 8.5-year visit, approximately one year prior to the administration of the NEPSY.

2.7. Statistical Analyses

The data were analyzed in multiple steps. In preliminary analyses, the distributional properties of the NEPSY dependent variables were evaluated using univariate analyses, and descriptive statistics for NEPSY variables and the sample's characteristics were calculated. The bivariate associations between IUCE and potential control variables, and IUCE and the NEPSY dependent variables were evaluated using correlations, *t*-tests, one-way ANOVA, and chi-square tests. A power analysis was also carried out.

The association between the ordinal IUCE variable (unexposed, lighter exposure, heavier exposure) and the NEPSY dependent variables was then evaluated in four successive linear regression models, with each model building on the prior one. The first model evaluated the bivariate association between IUCE and NEPSY outcomes (i.e., the five core domains and associated subtest scores). The remaining three regression models were multivariate. To limit the number of statistical tests, the dependent variables in the multivariate models were limited to the five NEPSY core domain scores and any subtest score that was associated with IUCE at a *p* level of .10 or less in the first model.

In the second model, the association between IUCE and NEPSY outcomes was re-evaluated controlling for intrauterine exposure to tobacco, marijuana, and alcohol, in addition to IUCE. These additional variables were added because prior research has shown that intrauterine exposure to these substances often co-occurs with IUCE and may or alter mask IUCE effects [3,44,75]. Moreover, each has been shown to alter children's neuropsychological functioning in multiple domains [52,96,110].

In the third model, four *a priori* biologic and social control variables were added to the variables in model 2: caregivers' education, custody arrangements (biological mother, kin caregiver, or non-kin foster/adoptive caregiver), children's sex, and prorated IQ. Each of these variables has been linked to children's general cognitive and neuropsychological functioning in both the broader child development literature [26,117,124] and the IUCE literature [3,23], including in prior research with the present cohort [13,48,113].

The fourth model built on the variables included in model 3. Additional maternal/caregiver and child control variables (listed in Tables 1 and 2) were evaluated for possible inclusion in the model, because they have been shown to be associated with IUCE and/or neuropsychological functioning in prior research; however, they have been less consistently or systematically evaluated, compared to the *a priori* variables included in model 3. Each variable was evaluated one-by-one in a separate multivariate regression for each NEPSY dependent variable. Any variable that changed the unadjusted parameter estimate (slope) for IUCE and a particular outcome by 10% or more was retained as an independent variable in that regression, in addition to the variables included in model 3. This approach provides the most valid estimate of the effect of the exposure of interest on outcome in behavioral teratology studies, such as this study; however, it does not identify which control variable, among those evaluated, is the strongest predictor of outcome [94]. Note that the specific variables added in model 4 could differ, depending on the specific dependent variable in question.

Prior to conducting the multivariate regression analyses (models 2-4), potential multicollinearity among the independent variables was examined by computing variance inflation factors (VIF) for each variable. In addition, the significance of potential interactions between IUCE and each control variable included in the models on the NEPSY outcome variables was examined. Interactions between IUCE and each control variable were tested on a one-by-one basis with each dependent variable using a significance level of 0.05. Any significant interaction terms were included in the model, and any not found to be statistically significant were not retained.

The statistical values generated in the multivariate linear regressions (models 2-4) were adjusted for level of IUCE and all other variables included in that model. Means and standard errors for any significant cocaine effect were computed from the estimated model parameters, adjusting for all other variables in the model. Findings are noted as statistically significant using an alpha level of .05 (two-tailed). Effect sizes for any significant or marginally significant IUCE effects in the one-way ANOVAs were calculated using eta-squared (η^2), with small effects described as 0.01; medium effects as 0.059; and large effects as 0.138 or higher [30]. For variables significantly or marginally associated with IUCE in the regression analyses, effect sizes for the post-hoc contrasts between the three IUCE groups were calculated using Cohen's *d*, defined as the difference between adjusted group means (unadjusted means in model 1) divided by the pooled standard deviation [30]. For Cohen's d, small effects are described as .20, medium effects as .50, and large effects as .80 or greater [30].

3. Results

3.1. Recruitment and Retention

Of the 252 newborns recruited in the original study at intake, 110 were lost to follow-up at the time of the 9.5-year visit (approximately 22% withdrew, 65% could not be reached, and 13% were unavailable for study at 9.5 years due to noncompliance or geographical unavailability, see [13,48,113] for further details). A total of 142 children in this high-risk, mobile cohort participated in the 9.5-year follow-up visit. Of these, five (3.5%) did not complete the NEPSY due to time constraints, scheduling conflicts, or child refusal. The remaining 137 (96.48%) were administered the NEPSY and comprised the present sample.

Results of bivariate analyses comparing the 137 children with NEPSY data to the 115 non-participants revealed no retention bias on the key study variables, including level of IUCE, prenatal exposure to tobacco, marijuana, or alcohol; birth mothers' age, education, race/ethnicity, parity, marital status, or receipt of public assistance; or children's sex, birth weight adjusted for gestational age, birth head circumference, or prorated IQ at 8.5 years. There was one exception: A lower percentage of immigrants were included among birth mothers in the participant group, compared to birth mothers in the non-participant group (12% versus 23%, $p = 0.03$).

3.2. Sample Characteristics

Of the 137 participants in the present sample, 90% were African American or African Caribbean in race/ethnicity, 52% of the children were male, and all were from urban, low-

income backgrounds. Seventy-one (52%) of the children had IUCE, and 66 (48%) were unexposed. Among the exposed children, 46 (65%) were classified as having lighter IUCE, and 25 (35%) were classified as having heavier IUCE. Attesting to the high-risk nature of this sample, nearly half (43%) of the children's current caregivers in this cohort reported that they or their child had been exposed to violence or victimized by the time of the 9.5-year visit.

Descriptive statistics for the sample's characteristics are presented for each IUCE group in Table 1 (maternal and current caregiver variables) and Table 2 (child variables). Results of one-way ANOVAs or chi square tests (as appropriate) indicated that level of IUCE was not significantly associated with birth mothers' race/ethnicity, years of completed education, marital status, employment status, or receipt of public assistance. Similarly, level of IUCE was not significantly associated with children's sex, age at the time of the 9.5-year visit, current grade in school, receipt of special education services (any), grade retention (any), history of violence exposure or victimization, or children's involvement with the birth father or father-figure.

Moreover, level of IUCE was not significantly associated with children's prorated IQ assessed at 8.5 years of age. On average, children in this cohort had prorated IQ scores that fell in the low average range (M IQ = 83.3). However, a higher-than-expected percentage of children in each IUCE group (6.2%) had a low IQ score (i.e., a standard score less than 70, which falls more than 2 SDs below the population mean), relative to the 2.3% one would expect, based on published age norms.

Consistent with findings in prior IUCE research, including in this cohort [10,16,47,80], birth mothers in both the lighter and heavier IUCE groups, compared with the unexposed group, were significantly older at the time of children's birth, more likely to have used tobacco, marijuana, or alcohol during pregnancy, and were less likely to be immigrants. At the time of the 9.5-year visit, the current caregivers of children in the unexposed group reported slightly more general psychological distress on the BSI than caregivers in the heavier or lighter IUCE groups. Moreover, children with either lighter or heavier IUCE, compared to unexposed children, were significantly lower in birth weight and more likely to be placed in the custody of caregivers other than the birth mother (kinship or non-kin foster/adoptive care) and to have experienced more changes in custodial arrangements since birth. The two exposure groups in the current sample did not differ significantly from each other on current or prior custodial arrangements; however, in earlier waves of data collection in this cohort, children with heavier IUCE were more likely than children with lighter IUCE to be placed in non-kin/adoptive care [47].

3.3. Descriptive Statistics for NEPSY Dependent Variables

Results of univariate analyses revealed that the five NEPSY core domain standard scores and their associated subtest scaled scores were normally distributed. When unadjusted means and standard deviations for the NEPSY scores were calculated for the three IUCE groups (unexposed, lighter exposed, heavier exposed), the average NEPSY scores in each group were generally within normal limits for age based on published norms. However, the mean scores for most variables fell below the population mean of 100. The unadjusted

means and standard deviations for each NEPSY variable, broken down by the three IUCE groups (unexposed, lighter exposed, and heavier exposed), results of one-way ANOVAs, and eta-squared values (effect size) for the overall IUCE effect are provided in Table 3. The one-way ANOVA results mirror the bivariate regression results (model 1), and are reported in section 3.6.1.

3.4. Power Analysis

Given the current sample size of 137, with 66, 46, and 25 children in the unexposed, lighter IUCE, and heavier IUCE groups, respectively, the regression analyses have 80% power to detect IUCE effects that have a medium or larger effect size (0.54 for the comparisons between the lighter exposed and unexposed groups, and 0.66 for the comparison between the heavier exposed and unexposed groups). These effects correspond to an 8.1 difference in mean NEPSY standard scores for the lighter versus unexposed comparisons, and 9.9 points for the heavier versus unexposed comparisons.

3.5. Regression Results

Regression results pertaining to the association between level of IUCE and the NEPSY dependent variables in each model are presented next. Any significant covariate effects observed in the multivariate models for particular NEPSY variables (models 2-4) are reported in a separate section. Due to space constraints and to increase clarity, Table 4 presents descriptive statistics and regression results only for NEPSY variables showing a significant or marginally significant bivariate association with IUCE in model 1. Unadjusted means and standard deviations by level of IUCE for these variables are provided for model 1, and least square means and standard errors are listed for models 2-4. Regression results for other NEPSY variables are provided in the Appendix.

3.5.1. Bivariate Association between IUCE and NEPSY Variables (Model 1)—

Mirroring the results of the one-way ANOVAs (Table 3), results of the bivariate regressions indicated that level of IUCE was not significantly associated with any of the five NEPSY core domain variables or most subscale scores. There were two notable exceptions. A significant main effect of level of IUCE on *Auditory Attention* scaled scores was found, with a medium effect size (see Table 3). Specifically, children with IUCE had lower *Auditory Attention* scaled scores than the unexposed children. Results of *a priori* contrasts comparing the two IUCE groups to the unexposed group showed that the scores in the lighter IUCE group were significantly lower than those in the unexposed group, with a moderate effect size, $d = -0.53$. In contrast, the heavier IUCE versus unexposed group contrast was not statistically significant, with a small effect size, $d = 0.04$. See Table 4a.

A similar pattern of results was observed for *Narrative Memory* scaled scores, although the overall IUCE effect in the bivariate regression (model 1) for this variable was only marginally significant ($p < .079$) with a small-to-medium effect size. Results of *a priori* contrasts comparing the two IUCE groups to the unexposed group showed that narrative memory scores children in the lighter exposed group were significantly lower than those in the unexposed group, with a small-to-moderate effect size, $d = -0.37$. In contrast, the scores

of children in the heavier exposed group did not differ significantly from those of children in the unexposed group, with a small effect size, $d = 0.11$. See Table 4b.

3.5.2. Multivariate Regression Results—There was no evidence of multicollinearity among the independent variables included in any of the multivariate models (no VIF exceeded 3.0). Moreover, no interaction terms between level of IUCE and other predictors (e.g., child sex) met criteria for inclusion in any multivariate model.

As was the case in the bivariate regressions (model 1), the results of the multivariate regressions indicated that IUCE was not significantly associated with any of the five NEPSY core domain variables or with most subtests, in any multivariate model. Two notable exceptions were the *Auditory Attention* and *Narrative Memory* tests.

3.5.2.1. Auditory Attention: When *Auditory Attention* scaled scores were evaluated in the multivariate regressions, the significant bivariate IUCE effect observed for this variable in model 1 remained statistically significant after covariate control in each subsequent multivariate model. As was the case in model 1, results of *a priori* contrasts comparing the two exposed groups to the unexposed group showed that the scores in the lighter IUCE group were significantly lower than those in the unexposed group in models 2 and 3, with moderate and small-to-moderate effect sizes, respectively (model 2, $d = -0.50$; model 3, $d = -0.45$). In model 4, the overall IUCE effect remained statistically significant, but the effect for the lighter/unexposed contrast was reduced to marginal significance ($p = 0.058$) with a small-medium effect size ($d = -.43$). In contrast, the heavier exposed versus unexposed group contrasts for *Auditory Attention* were not statistically significant in any model, and all had a small effect size (model 2, $d = 0.13$; model 3 $d = 0.04$, model 4 $d = 0.11$). See Table 4a.

To explore the *Auditory Attention* finding further, the association of level of IUCE with scores from each of the two tasks comprising this subtest (*Attention Task* and *Response Set*) was examined separately, using the same analytic approach used for the other NEPSY dependent variables, described in section 2.7. Unadjusted means and standard deviations for these subtests are presented in Table 3, and full regression results are provided in the Appendix. IUCE was significantly associated with poorer performance on the *Attention Task* in every model (IUCE effect in model 1: $p = 0.0051$; model 2: $p = 0.0076$, model 3: $p = 0.0311$, model 4: $p = 0.022$). As was the case with the composite *Auditory Attention* variable, results of *a priori* contrast tests indicated that children with lighter IUCE had significantly poorer performance on the *Attention Task* than unexposed children in all models. However, for the more complex and demanding *Response Set* task, which requires impulse control and set shifting for successful performance, children's average scaled scores in each IUCE group were lower than on the *Attention Task*, and no significant IUCE effects were observed in any model.

3.5.2.2. Narrative Memory: Significant IUCE effects were also observed for *Narrative Memory* subscale scores in the multivariate analyses (Table 4b). The IUCE effect for this variable moved from marginal significance in model 1 to statistical significance in model 2, after control for intrauterine exposure to tobacco, alcohol, and marijuana, and retained its

statistical significance in each subsequent multivariate model, which controlled for additional maternal/caregiver and child variables. Results of *a priori* contrasts comparing the two IUCE groups to the unexposed group showed that the average *Narrative Memory* scores in the lighter IUCE group were significantly lower than those in the unexposed group, with a medium effect size in each multivariate model (model 2, d = -0.55; model 3, d = -0.58, model 4 d = -0.59).

Notably, the heavier IUCE versus unexposed group contrast for *Narrative Memory* was not statistically significant in any model. However, the heavier/unexposed contrast became marginally significant in model 3 (p = 0.057) and remained marginally significant after controlling for additional variables in model 4 (p = 0.087). Moreover, the effect sizes for the heavier exposed/unexposed contrast in each multivariate model fell in the medium to medium-high range (model 2, d = 0.67; model 3 d = -.0.49, model 4 d = -0.47).

3.6. Covariate Effects

In contrast to the relatively few significant IUCE effects observed for the NEPSY dependent variables in these analyses (see section 3.5), many maternal, caregiver, and child variables were found to be significant predictors of children's neuropsychological performance on the NEPSY, controlling for level of IUCE and other variables in the model. For the two NEPSY subtests significantly associated with IUCE in the current analyses (*Auditory Attention* and *Narrative Memory*), the following covariate effects were observed: Female sex was associated higher scores on *Response Set* (but not on the simpler *Attention Task*) (p = 0.01) and higher *Narrative Memory* scores (p = 0.003). Higher caregiver education was also associated with higher *Narrative Memory* scores (p = 0.003). In turn, exposure to violence or victimization was associated with lower *Auditory Attention* scores. Paradoxically, intrauterine tobacco exposure predicted higher scores on the *Narrative Memory* subtest (p = 0.011). Higher child prorated IQ assessed at the 8.5 year visit was significantly associated with higher scores on all NEPSY dependent variables ($p < 0.05$).

4. Discussion

The goal of the current analysis was to evaluate whether level of IUCE is associated with multiple dimensions of neuropsychological functioning at preadolescence assessed using a single age-referenced neuropsychological assessment, the NEPSY [71], before and after controlling for relevant covariates. Although all NEPSY tests were evaluated in the present analyses, we were particularly interested in evaluating IUCE effects on specific dimensions of neuropsychological function that are most often associated with IUCE in recent reviews (i.e., language, attention, and memory) [3,23] . Moreover, these measures are linked to children's general cognitive functioning in the cognitive neuroscience literature [4,9,106,130].

Our findings are consistent with a growing body of results in the animal and human literatures showing that IUCE is associated with alterations in auditory processes [27,74,86,108,122,131,134]. Specifically, results of our covariate-controlled analyses show that IUCE is associated with mild compromises on two age-referenced indices of auditory processes assessed by the NEPSY at preadolescence: *Auditory Attention* and *Narrative*

Memory. Contrary to our expectations and findings in prior reports (e.g., [1,7,12,40]), level of IUCE in the present cohort was not significantly associated with compromised scores on the NEPSY *Visual Attention* subscale, or with the *Language*, *Sensorimotor*, or *Visuospatial* core domains, or any of their associated subscales.

4.1. Auditory Attention

Regression results show that level of IUCE is associated with poorer Auditory Attention scores on the NEPSY at age 9.5 years in this low-income urban cohort, both before and after covariate control. Notably, when the two tasks comprising the *Auditory Attention* subtest (*Attention Task* and *Response Set*) were evaluated separately, IUCE was associated only with the first, a test of simple sustained auditory attention. When the cognitive load increased in the second task, and children were required to shift set and control impulsivity for accurate performance (a more complex task for all), the averages scores of children in each group decreased (average scores in each group were well below the population mean), and no significant IUCE effects were observed. A similar finding showing diminished performance on simple neuropsychological tasks requiring fundamental (“bottom-up”) processing was reported by Fried for adolescents with prenatal tobacco exposure [49].

Difficulty on attention tasks, whether simple or complex, is worrisome because attention problems may contribute to compromised performance on more complex cognitive, language, memory, and learning tasks, with implications for academic functioning and psychosocial well-being [107]. Further evaluation of how IUCE-related attention problems contribute to children's performance on higher-order neuropsychological tasks at preadolescence and beyond is warranted [107,115].

4.2. Narrative Memory

Our analyses show that level of IUCE is associated with mild decrements in children's scores on *Narrative Memory*, a task evaluating children's verbal memory for brief stories (narratives) read to them by the examiner. In contrast to the findings for *Auditory Attention*, however, the IUCE effect observed for *Narrative Memory* was only marginally significant in the bivariate analyses (model 1), and did not reach statistical significance until intrauterine exposures to tobacco, alcohol, and marijuana were statistically controlled in model 2. This finding suggests that the effect of IUCE in model 1 may have been suppressed by children's intrauterine poly-drug exposure [100] . Consistent with our findings for *Auditory Attention*, however, the IUCE effect for *Narrative Memory* remained significant after control for additional relevant maternal/caregiver and child variables in the two subsequent multivariate models.

Although the specific cognitive demands placed on the child by each test differ substantially, both the *Narrative Memory* and *Auditory Attention* tasks require sustained auditory attention, auditory information processing, as well as verbal working memory skills for successful performance [68], and we speculate that these skills contribute to the mild delays in language performance observed for many school-aged children with IUCE, both in this cohort and in the broader IUCE literature [10,13,80]. Identifying IUCE effects on specific neuropsychological skills and their associations with language skills is an important

endeavor, as it may inform future research by suggesting possible mechanisms underlying the IUCE-related variations in school-aged children's language skills reported in prior research with this cohort [13] and in other prospective studies [10,80]. Whether neuropsychological processes such as auditory attention or narrative memory mediate the association between IUCE and children's language functioning at school-age or during adolescence also warrants further evaluation.

4.3. Level of IUCE

The IUCE effects on *Auditory Attention* and *Narrative Memory* scores observed in this low-income urban cohort of preadolescents do not follow the expected ordinal dose-dependent pattern. For both NEPSY variables, the contrasts between the lighter IUCE and unexposed groups were statistically significant in each multivariate model, with medium effect sizes, whereas the contrasts between the heavier IUCE and unexposed groups were not. This suggests that a behavioral teratology explanation for these findings is not sufficient. Notably, the effect sizes for the heavier IUCE/unexposed group contrasts for the two dependent variables were not identical. For *Auditory Attention*, the effect sizes for this contrast were small in each model, whereas for *Narrative Memory*, these effect sizes were consistently in the medium or medium-large range after covariate control. In a larger sample, the heavier IUCE/unexposed contrast for *Narrative Memory* may have reached statistical significance. Alternatively, there could be unmeasured genetic variability in the three IUCE groups, or the time of exposure to cocaine during gestation may be more important than the dosage [23,43,75,90,109]. Further evaluation of auditory attention and narrative memory processes in larger samples of school-aged children and adolescents varying in the level and timing of IUCE is needed.

The lack of a clear dose-dependent IUCE effect in these analyses and at this age may also reflect the role of unmeasured biological and environmental risk and protective factors associated with children's custodial arrangements. Children in the two IUCE groups in the present sample differed significantly from unexposed children in current custodial arrangements and the number of caregiver changes experienced since birth, but did not differ significantly from each other. However, this was not the case at earlier waves of data collection in this cohort. During infancy and toddlerhood, a time when brain development may be especially sensitive to environmental input [43], children in the heavier IUCE group were more likely than children with lighter IUCE to receive non-kin foster/adoptive care [47]. Although results pertaining to the effects of different types of custodial arrangements on children's functioning in the broader literature are not consistent [126-128], non-kin foster/adoptive caregivers in the IUCE literature typically differ from birth mothers or kinship caregivers on several dimensions that may influence children's outcomes. Specifically, non-kin foster/adoptive caregivers are more likely than birth mothers or kinship caregivers to be married, to have completed more years of education, to provide a more stimulating home environment for children, and to live in less dangerous neighborhoods [13,22,124,127]. In many studies, these differences are associated with more optimal child language and cognitive outcomes [13,18,26,59,124,140]. In the present sample, non-maternal custodial arrangements were significantly associated with intrauterine exposure to tobacco, alcohol, and marijuana, and lower child birth weight, in addition to IUCE.

Although we carefully controlled for these and other biological and environmental variables in the multivariate regressions, unmeasured child, caregiver, or demographic differences (e.g., quality of the home environment) associated with children's custodial arrangements in the three IUCE groups may have contributed to our specific pattern of findings.

Contrary to our expectations and prior findings for language outcomes in this cohort at school-age [13], there were no significant interactions of level of IUCE with the other predictors in the multivariate regressions, such as child sex, age at test, or birth weight, on children's neuropsychological test scores. Although the reason for the lack of significant interactions is not known, we speculate that the moderating effects of different control variables on IUCE effects may vary at different ages and with the use of different instruments to measure neuropsychological functioning [3,23].

4.4. Effects of Other Biological and Social Variables on Neuropsychological Performance

Consistent with prior findings in this and other cohorts [3,6,10,13,17,33,73,124], a wide array of biologic and environmental control variables exerted significant, independent effects on children's neuropsychological functioning as assessed with the NEPSY in the current study, regardless of IUCE status. For the two NEPSY variables showing significant IUCE effects, female sex predicted higher scores on the *Response Set* subtest of the *Auditory Attention* scale, a complex task requiring impulse control and set-shifting, in addition to sustained auditory attention. Both female sex and higher caregiver education predicted higher scores on the *Narrative Memory* scale. Moreover, consistent with extant literature on environmental risk and trauma exposure [8,13,23,69], any child or caregiver violence exposure or victimization during the past year was associated with poorer child performance on the *Auditory Attention* subtest. Children's general intelligence, as indexed by a prorated IQ score assessed one year prior to the NEPSY evaluation, contributed to their neuropsychological performance on all NEPSY dependent measures.

Paradoxically, and contrary to expectations based on prior literature [54,55,61], intrauterine exposure to tobacco was linked to better performance on the *Narrative Memory* subtest. Although the reason for this counter-intuitive finding is not known, similar paradoxical effects were found in prior research with this cohort at different ages [13,47,113]. Some have suggested that, in the context of prenatal exposure to other substances, prenatal tobacco exposure may serve a protective function for some aspects of neuropsychological functioning, or may reflect gene-environment transactions not assessed in the present study [39,53,57,114].

4.5. Strengths and Limitations

This study has both strengths and limitations. Among its strengths are its prospective longitudinal design, use of biological markers (i.e., meconium and urine assays) to ascertain level of IUCE in the newborn period, inclusion of a psychometrically sound battery of neuropsychological assessments, comprehensive caregiver interviews and questionnaires administered at multiple time points, and the use of masked examiners. To evaluate multiple aspects of children's neuropsychological functioning at the 9.5-year visit, we used a single age-referenced instrument, the NEPSY. This is advantageous because it provides a diverse

set of neuropsychological measures that were co-normed on the same national standardization sample. A drawback is that this single instrument may not measure all aspects of neuropsychological functioning, including those that may be relevant to language development, and not all measures included in this instrument may have equal sensitivity to IUCE effects. Future studies should evaluate the effects of IUCE on measures tapping a broader spectrum of neuropsychological functions, especially auditory information processing and verbal memory skills, and ascertain their links to children's language and academic performance at later ages.

In addition, our analyses were based on neuropsychological test scores obtained from a relatively homogeneous sample of low-income, urban, mostly African American/Caribbean preadolescents who were followed prospectively from birth. This approach offers both strengths and limitations. First, studies of neuropsychological functioning in non-clinically referred, at-risk low-income samples of preadolescents are relatively rare in the literature. These studies are important because they can shed light on important aspects of these children's neuropsychological functioning relevant to their school success and psychosocial well-being, with implications for practice and policy [37,132]. However, the results may not generalize to all children with IUCE, such as those born prematurely, those from different racial/ethnic or socio-economic backgrounds, or those living in rural or suburban areas. Replication in more heterogeneous samples is needed. Further evaluation of neuropsychological functioning at later ages is also needed, when academic demands become more complex and challenging.

Another limitation is that there was significant attrition in this high-risk, highly mobile cohort over time. However, this should not affect interpretation of the current findings because there was no evidence for differential attrition (retention bias) on any of the key study variables evaluated in this analysis.

A related limitation is the current sample's relatively small size at the 9.5-year visit (N = 137), which may have constrained statistical power. Our analyses had adequate power to detect medium or higher IUCE effects, but smaller effects may have gone undetected. Although the overall IUCE effects on *Auditory Attention* and *Narrative Memory* scores identified in our study were small to moderate in magnitude, these findings are likely to be reliable. Moreover, results of *a priori* contrasts between the lighter and unexposed groups for both variables, and between the heavier and unexposed groups for narrative memory had effect sizes in the medium and medium-large range. Furthermore, a large number of significant effects of biological and environmental control variables on children's neuropsychological functioning were found in the current sample, underscoring the plausibility of our measurements.

5. Conclusions and Implications

The findings from this study suggest that level of IUCE is associated with subtle, specific effects on auditory processes (i.e., *Auditory Attention* and *Narrative Memory* scores) in preadolescents from low-income, urban backgrounds. However, these effects do not appear

to be dose-dependent, and children's neuropsychological functioning is also altered by a wide array of other biologic and environmental variables.

Regardless of IUCE status, attention and memory problems are concerning because they predict academic achievement in both typical developing [25] and clinically referred populations [112]. When children with a history of IUCE present with attention, memory, or other learning problems, clinicians and educators should not assume that IUCE is the sole causative factor. Rather, they should evaluate children's functioning with comprehensive neurodevelopmental assessments that include measures of auditory processing. They also would do well to conduct a careful assessment in early life to help caregivers identify and minimize exposure to remediable risk factors that may undermine healthy neuropsychological outcomes, and promote access to protective factors that may contribute to children's positive development regardless of prenatal history [21].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

This appendix includes the results of linear regressions evaluating the association between intrauterine cocaine exposure and NEPSY outcomes before and after covariate control (i.e., all Core Domain scores, plus any subtest scores associated with intrauterine cocaine exposure at $p < .10$ in bivariate analyses), before and after covariate control.

Table A

Results of Linear Regressions Evaluating the Association between Intrauterine Cocaine Exposure (IUCE) and NEPSY[*] Core Domain and Subtest Scores[**] before and after Covariate Control (Models 1-4[a–d])

NEPSY Measure	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
1. Attention/Executive Functions				
Core Domain	M (SD)[e]; *p-value*	LSM (SE)[f]; *p*-value	LSM (SE); *p*-value	LSM (SE); *p*-value
Heavier IUCE	90.56 (11.89); 0.597	91.69 (2.77); 0.97	90.06 (2.78); 0.590	90.21 (2.64); 0.484
Lighter IUCE	87.72 (14.04); 0.072	87.92 (1.91); 0.171	88.22 (1.88); 0.163	87.16 (1.82); 0.037
Unexposed	92.14 (11.84)	91.56 (1.71)	91.99 (1.73)	92.55 (1.68)
	IUCE main effect, p=0.20	IUCE main effect, p=0.30	IUCE main effect, p=0.37	IUCE main effect, p=0.11

NEPSY Measure	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
	Model F (2, 133) = 1.65, *p*=0.20	*Model F* (5, 130) = 0.95, *p*=0.45	*Model F* (10, 124) = 2.15, *p*= 0.03	*Model F* (12, 118)= 3.48, *p*< 0.001
	R^2=0.02	R^2=0.035	R^2=0.148	R^2=0.228
1a.*Auditory Attention* subtest	M (SD)[e]; *p-value*	LSM (SE)[f]; *p*-value	LSM (SE); *p*-value	LSM (SE); *p*-value
Heavier IUCE	9.08 (1.26); 0.855	9.21 (0.49); 0.637	9.01 (0.49); 0.872	9.11 (0.50); 0.717
Lighter IUCE	7.78 (2.74); 0.006	7.79 (0.34); 0.018	7.88 (0.34); 0.038	7.89 (0.35); 0.058
Unexposed	8.98 (2.09)	8.92 (0.30)	8.91 (0.31)	8.87 (0.32)
	IUCE main effect, *p*=0.011	IUCE main effect, *p*=0.014	IUCE main effect, *p*=0.044	IUCE main effect, *p*=0.044
	Model F (2, 131) = 4.65, *p*= 0.011	*Model F* (5, 128) = 2.01, *p*= 0.082	*Model F* (10, 122) = 2.28, *p*= 0.018	*Model F* (12, 118)= 2.13, *p*= 0.019
	R^2=0.066	R^2=0.073	R^2=0.157	R^2=0.176
1ai. *Attention task* (part 1 of *Auditory Attention* subtest)	M (SD)[e]; *p-value*	LSM (SE)[f]; *p*-value	LSM (SE); *p*-value	LSM (SE); *p*-value
Heavier IUCE	9.40 (1.94); 0.950	9.76 (0.55), 0.465	9.66 (0.58), 0.506	9.87 (0.59), 0.319
Lighter IUCE	7.89 (3.21); 0.002	7.95 (0.39), 0.016	8.09 (0.39), 0.05	8.06 (0.40), 0.083
Unexposed	9.44 (2.18)	9.25 (0.34)	9.17 (0.36)	9.00 (0.38)
	IUCE main effect, *p*=0.0005	IUCE main effect, *p*=0.0076	IUCE main effect, *p*=0.031	IUCE main effect, *p*=0.0234
	Model F (2, 131) =5.49, *p*=0.0051	*Model F* (5, 128) =2.76, *p*=0.021	*Model F* (10, 122) =2.02, *p*=0.037	*Model F* (12, 120) =2.08, *p*=0.023
	R^2=0.077	R^2=0.097	R^2=0.142	R^2=0.172
2.Language Core Domain	M (SD)[e]; *p-value*	LSM (SE)[f]; *p*-value	LSM (SE); *p*-value	LSM (SE); *p*-value
Heavier IUCE	89.12 (13.17); 0.983	91.00 (3.30); 0.509	86.63 (2.87); 0.415	86.63 (2.87); 0.415
Lighter IUCE	86.12 (14.04); 0.395	87.02 (2.27); 0.689	87.46 (1.93); 0.434	87.46 (1.93); 0.434
Unexposed	89.19 (16.46)	88.28 (2.02)	89.63 (1.77)	89.63 (1.77)
	IUCE main effect, *p*=0.669	IUCE main effect, *p*=0.590	IUCE main effect, *p*=0.652	IUCE main effect, *p*=0.652
	Model F (2, 134) = 0.40, *p*= 0.669	*Model F* (5, 131) = 0.77, *p*= 0.570	*Model F* (10, 125) = 6.96, *p*< 0.001	*Model F* (10, 125) = 6.96, *p*< 0.001
	R^2 =0.006	R^2=0.029	R^2=0.358	R^2=0.358
3.Sensorimotor Core Domain	M (SD)[e]; *p-value*	LSM (SE)[f]; *p*-value	LSM (SE); *p*-value	LSM (SE); *p*-value
Heavier IUCE	80.33 (12.28); 0.437	80.22 (3.13); 0.481	77.12 (3.12); 0.065	75.45 (3.29); 0.017
Lighter IUCE	83.73 (14.06); 0.759	83.71 (2.13); 0.797	83.26 (2.07); 0.674	82.58 (2.14); 0.299
Unexposed	82.91 (14.27)	82.96 (1.87)	84.50 (1.87)	85.86 (2.03)
	IUCE main effect, *p*=0.619	IUCE main effect, *p*=0.638	IUCE main effect, *p*=0.154	IUCE main effect, *p*=0.054

NEPSY Measure	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
	Model F (2, 132) = 0.48, *p*= 0.619	*Model F* (5, 129) = 0.19, *p*= 0.965	*Model F* (10, 123) = 2.10, *p*= 0.029	*Model F* (16, 111) = 1.64, *p*= 0.069
	R^2=0.007	R^2=0.007	R^2=0.146	R^2=0.192
4.Visuospatial Core Domain	M (SD)[e]; *p-value*	LSM (SE)[f]; *p*-value	LSM (SE); *p*-value	LSM (SE); *p*-value
Heavier IUCE	95.56 (15.79); 0.519	97.46 (3.61); 0.198	95.42 (3.37); 0.415	95.42 (3.37); 0.415
Lighter IUCE	91.09 (17.79); 0.545	92.07 (2.49); 0.897	92.51 (2.27); 0.855	92.51 (2.27); 0.855
Unexposed	93.03 (16.14)	91.63 (2.20)	91.92 (2.07)	91.92 (2.07)
	IUCE main effect, *p*=0.554	IUCE main effect, *p*=0.382	IUCE main effect, *p*=0.697	IUCE main effect, *p*=0.697
	Model F (2, 134) = 0.59, *p* = 0.554	*Model F* (5, 131) = 1.21, *p* = 0.310	*Model F* (10, 125) = 4.64, *p*< 0.001	*Model F* (10, 125) = 4.64, *p*< 0.001
	R^2 = 0.009	R^2=0.044	R^2=0.271	R^2=0.271
5.Memory/Learning Core Domain	M (SD)[e]; *p-value*	LSM (SE)[f]; *p*-value	LSM (SE); *p*-value	LSM (SE); *p*-value
Heavier IUCE	101.24 (19.38); 0.511	101.66 (3.53); 0.515	97.35 (3.40); 0.543	99.44 (3.41); 0.245
Lighter IUCE	95.07 (15.88); 0.242	94.76 (2.43); 0.233	95.09 (2.29); 0.136	95.68 (2.26); 0.268
Unexposed	98.73 (15.14)	98.78 (2.16)	100.01 (2.09)	99.32 (2.07)
	IUCE main effect, *p*=0.271	IUCE main effect, *p*=0.202	IUCE main effect, *p*=0.324	IUCE main effect, *p*=0.427
	Model F (2, 134) = 1.32, *p*= 0.271	*Model F* (5, 131) = 1.26, *p*= 0.285	*Model F* (10, 125) = 3.56, *p*< 0.001	*Model F* (11, 123) = 3.63, *p*< 0.001
	R^2 = 0.019	R^2=0.046	R^2=0.222	R^2=0.245
5a.*Narrative Memory* subtest	M (SD)[e]; *p-value*	LSM (SE)[f]; *p*-value	LSM (SE); *p*-value	LSM (SE); *p*-value
Heavier IUCE	9.44 (3.43); 0.646	8.80 (0.72); 0.464	8.02 (0.67); 0.057	8.11 (0.72); 0.087
Lighter IUCE	7.83 (3.33); 0.548	7.62 (0.50); 0.008	7.71 (0.45); 0.003	7.71 (0.47); 0.004
Unexposed	9.08 (3.34)	9.47 (0.44)	9.67 (0.42)	9.69 (0.44)
	IUCE main effect, *p*=0.079	IUCE main effect, *p*=0.026	IUCE main effect, *p*=0.011	IUCE main effect, *p*=0.014
	Model F (2, 133) = 2.58, *p*= 0.079	*Model F* (5, 130) = 2.22, *p*= 0.056	*Model F* (10, 124) = 5.16, *p*< 0.001	*Model F* (12, 118) = 4.36, *p*< 0.001
	R^2 = 0.037	R^2=0.079	R^2=0.294	R^2=0.336

* NEPSY=NEPSY: A Developmental Neuropsychological Assessment [71]

** Regression results are presented for all 5 NEPSY core domains and for those subtests showing a significant or marginally significant ($p < .10$) association with IUCE.

[a] Model 1 independent variable: IUCE only

[b] Model 2 independent variables: IUCE plus prenatal exposure to tobacco, marijuana, and alcohol

[c] Model 3 independent variables: Model 2 variables plus caregiver's education, child's sex, IQ, and custody arrangements

[d] Model 4 independent variables: Model 3 variables plus any control variable in Table 1 or 2 changing the magnitude of the association between IUCE and NEPSY outcome ≥ 10%, [94]

[e] *M* (*SD*) = arithmetic mean (standard deviation)

[f] LSM (SE) = least square mean (standard error), adjusted for all variables in the model

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Abbreviations

IUCE	Intrauterine cocaine exposure
NEPSY	*NEPSY-A Developmental Neuropsychological Assessment*

Highlights

- Neuropsychological skills contribute to higher-level cognitive processes.
- Does prenatal cocaine exposure alter neuropsychological skills at preadolescence?
- Multiple neuropsychological skills were assessed at 9.5 years using the *NEPSY*.
- Prenatal cocaine exposure predicted poorer auditory attention and narrative memory.
- Effects were small and did not follow the expected dose-dependent pattern.

Table 1

Maternal and Caregiver Characteristics by Level of Intrauterine Cocaine Exposure (*N* = 137)

	Level of Intrauterine Cocaine Exposure			Bivariate *p*-value[a]
	Unexposed (*n*=66)	Lighter Exposed (*n* =46)	Heavier Exposed (*n* =25)	
	% or M (SD)[b]	% or M (SD)	% or M (*SD*)	
Birth Mother				
African-American/Caribbean race/ethnicity (%)	90.9%	87%	92%	0.751
US-born (%)	75.8%	97.8%	100%	< 0.001
Primiparous (%)	45.4%	26.1%	36%	0.112
Age (years) at child's birth	25.5 (5.6)	27.9 (4.5)	27.3 (3.7)	0.033
Education (years) at child's birth	11.6 (1.4)	11.6 (1.4)	11.4 (1.0)	0.681
Prenatal substance use				
Average daily number of prenatal cigarettes	3.1 (7.8)	6.2 (6.7)	11.4 (14.0)	0.001
Average daily volume of alcohol during last 30 days of pregnancy	0.0 (0.0)	0.3 (1.2)	1.2 (3.2)	0.006
Prenatal marijuana use (any) (%)	10.6%	30.4%	36.0%	0.008
Current Caregiver at 9.5-Year Visit				
Education (years)	12.5 (1.8)	11.9 (1.6)	12.7 (2.4)	0.133
Married or living with partner (%)	47.4%	31%	28.6%	0.151
Employed (%)	59.7%	50%	57.1%	0.628
Receiving public assistance[c] (%)	43.9%	64.3%	57.1%	0.122
Custody arrangements at 9.5-year visit (%)				<0.001
Birth mother	93.9%	63%	48%	
Kinship caregiver	4.6%	19.6%	40%	
Non-kin foster caregiver	1.5%	17.4%	12%	
Number of changes in primary caregiver since child's birth	0.4 (1.2)	2.2 (2.2)	2.5 (2.4)	<0.001
Birth mother is child's primary caregiver since the child's birth (%)	83.3%	41.3%	32%	<0.001
Current caregiver's substance use				
Average daily number of cigarettes	4.0 (13.7)	3.9 (6.4)	5.1 (7.4)	0.907
Any alcohol (past 30 days) (%)	33.3%	31%	28.6%	0.916
Any marijuana (past 30 days) (%)	7%	7.1%	4.8%	0.928

	Level of Intrauterine Cocaine Exposure			
	Unexposed (*n*=66)	Lighter Exposed (*n* =46)	Heavier Exposed (*n* =25)	Bivariate *p*-value[a]
	% or M (SD)[b]	% or M (SD)	% or M (*SD*)	
Any cocaine or other illicit drug use (past 30 days) (%)	0%	0%	0%	1.0
Current caregiver's psychological distress (BSI GSI)	0.3 (0.4)	0.2 (0.2)	0.2 (0.2)	0.025

[a] Based on chi square or one-way ANOVA, as appropriate

[b] *M* (*SD*) = arithmetic mean (standard deviation)

[c] Any receipt of food stamps, housing assistance or Transitional Assistance to Needy Families

[d] BSI = Brief Symptom Inventory; GSI = Global Severity Index

Table 2
Children's Characteristics by Level of Intrauterine Cocaine Exposure (*N* = 137)

	Level of Intrauterine Cocaine Exposure			Bivariate *p*-value[a]
	Unexposed (*n*=66)	Lighter Exposed (*n* 46)	Heavier Exposed (*n* =25)	
	% or *M (SD)*[b]	% or *M (SD)*	% or M (*SD*)	
Male sex (%)	53%	50%	52%	0.951
Birth weight (z-score[c])	-0.1 (1.0)	-0.7 (0.7)	-1.0 (0.7)	<0.001
Maximum blood lead level (micrograms per deciliter) through 4 years of age	9.5 (4.9)	9.3 (4.3)	11.3 (8.4)	0.422
Preschool enrichment experience (e.g., Head Start) (%)	50%	55.6%	44%	0.642
Age at 9.5-year visit	9.8 (0.6)	9.8 (0.4)	9.2 (0.4)	0.651
Grade in school at 9.5-year visit	4.5 (1.0)	4.4 (0.7)	4.6 (0.8)	0.700
General intelligence Prorated IQ[d] at 8.5-year visit	90.7 (15.0)	86.2 (14.9)	92.1 (12.7)	0.222
Low IQ (< 70) (%)	6%	9.8%	0%	0.461
Special education services or grade retention by 9.5 years (any, %)	36.4%	39.1%	16%	0.115
Child has contact with father or father figure (%)	46.2%	45.7%	48%	0.982
Exposure to violence or victimization				
EVI[e] (any caregiver or child, caregiver report, %)	40.6%	26.1%	60%	0.113
VEX-R[f] total score (child report)	14.8 (12.1)	15.4 (12.0)	16.5 (11.6)	0.84
Child's depressive symptoms				
CDI[g] total score, child report	5.1 (5.3)	5.5 (6.5)	4.8 (5.4)	0.889

[a] Based on chi square or one-way analysis of variance (ANOVA), as appropriate

[b] *M* (*SD*) = Arithmetic mean (standard deviation);

[c] Adjusted for gestational age and sex

[d] Wechsler Intelligence Test for Children (WISC-IV);

[e] EVI: Exposure to Violence Inventory;

[f] VEX-R: Violence Exposure Scale-Revised (VEX-R);

[g] Children's Depression Inventory (CDI)

Table 3

Descriptive Statistics for NEPSY[a] variables by Level of Intrauterine Cocaine Exposure and One-Way ANOVA Results

	Level of Intrauterine Cocaine Exposure				
NEPSY Variable	**Unexposed**	**Lighter Exposed**	**Heavier Exposed**	**η^2***	***p*-value**
1. Attention/Executive Function Core Domain					
n	65	46	25	0.024	0.2
Mean (standard score)	92.14	87.72	90.56		
Standard Deviation	11.84	14.04	11.90		
1a. Tower subtest					
n	66	46	25	0.006	0.66
Mean (scaled score)	9.21	8.72	8.88		
Standard Deviation	2.55	3.19	3.18		
1b. Visual Attention subtest					
n	66	46	25	0.002	0.89
Mean (scaled score)	8.67	8.61	8.36		
Standard Deviation	2.88	2.18	3.04		
1c. Auditory Attention subtest					
n	64	45	25	0.066	0.01[b]
Mean (scaled score)	8.98	7.78	9.08		
Standard Deviation	2.09	2.74	1.26		
1ci. Attention task (part 1 of Auditory Attention subtest)					
n	64	45	25	0.077	0.005[c]
Mean (scaled score)	9.44	7.89	9.40		
Standard Deviation	2.19	3.21	1.94		
1cii. Response set (part 2 of Auditory Attention subtest)					
n	64	45	25	0.030	0.13
Mean (scaled score)	8.67	7.93	8.80		
Standard Deviation	2.01	2.52	1.47		
2. Language Core Domain					
n	66	46	25	0.006	0.67
Mean (standard score)	89.20	86.72	89.12		

	Level of Intrauterine Cocaine Exposure				
NEPSY Variable	**Unexposed**	**Lighter Exposed**	**Heavier Exposed**	**η^2***	***p*-value**
Standard Deviation	16.46	14.05	13.17		
2a. Speed Naming subtest					
n	66	45	25	0.020	0.27
Mean (scaled score)	8.47	8.24	9.40		
Standard Deviation	2.98	3.11	2.33		
2b. Phonological Processing subtest					
n	66	46	25	0.011	0.48
Mean (scaled score)	7.95	7.41	8.08		
Standard Deviation	2.77	2.73	2.14		
2c. Comprehension of Instruction subtest					
n	66	46	25	0.001	0.91
Mean (scaled score)	8.15	8.04	8.40		
Standard Deviation	3.53	3.16	3.35		
3. Sensorimotor Core Domain					
n	66	45	24	0.007	0.62
Mean (standard score)	82.91	83.73	80.33		
Standard Deviation	14.27	14.06	12.28		
3a. Fingertip Tapping subtest					
n	65	45	25	0.009	0.57
Mean (scaled score)	6.82	7.24	7.56		
Standard Deviation	3.03	3.21	3.50		
3b. Imitating Hand Positions subtest					
n	65	45	25	0.008	0.58
Mean (scaled score)	7.94	8.16	7.44		
Standard Deviation	2.84	2.71	2.45		
3c. Visuomotor Precision subtest					
n	65	45	24	0.010	0.51
Mean (scaled score)	8.23	7.96	7.42		
Standard Deviation	2.97	3.15	2.39		
4. Visuospatial Core Domain					

	Level of Intrauterine Cocaine Exposure				
NEPSY Variable	**Unexposed**	**Lighter Exposed**	**Heavier Exposed**	**η^2***	***p*-value**
n	66	46	25	0.009	0.55
Mean (standard score)	93.03	91.09	95.56		
Standard Deviation	16.15	17.79	15.79		
4a. Arrows subtest					
n	66	46	25	0.007	0.61
Mean (scaled score	8.08	7.93	8.72		
Standard Deviation	3.08	3.35	3.75		
4b. Design Copying subtest					
n	66	45	25	0.006	0.68
Mean (scaled score)	9.82	9.29	9.80		
Standard Deviation	3.20	3.58	2.90		
5. Memory and Learning Core Domain					
n	66	46	25	0.019	0.27
Mean (standard score)	98.73	95.07	101.24		
Standard Deviation	15.14	15.88	19.38		
5a. Memory for Faces subtest					
n	66.00	46.00	25.00	0.002	0.88
Mean (scaled score)	11.52	11.50	11.88		
Standard Deviation	3.15	3.38	3.41		
5b. Memory for Names subtest					
n	65	45	25	0.004	0.76
Mean (scaled score)	8.85	8.60	9.16		
Standard Deviation	3.00	2.84	3.54		
5c. Narrative Memory subtest					
n	65	46	25	0.039	0.07
Mean (scaled score)	9.09	7.83	9.48		
Standard Deviation	3.32	3.33	3.40		

Table 4

Results of Linear Regressions Evaluating the Association between Level of Intrauterine Cocaine Exposure (IUCE) and NEPSY* *Auditory Attention* and *Narrative Memory* Subtest Scaled Scores before and after Covariate Control (Models 1-4[a–d])

NEPSY Variable	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d,e]
4a. *Auditory Attention* subtest	M (SD)[f]; *p*-value	LSM (SE)[g]; *p*-value	LSM (SE); *p*-value	LSM (SE); *p*-value
Heavier IUCE	9.08 (1.26); 0.855	9.21 (0.49); 0.637	9.01 (0.49); 0.872	9.11 (0.50); 0.717
Lighter IUCE	7.78 (2.74); 0.006	7.79 (0.34); 0.018	7.88 (0.34); 0.038	7.89 (0.35); 0.058
Unexposed	8.98 (2.09)	8.92 (0.30)	8.91 (0.31)	8.87 (0.32)
	IUCE main effect, p=0.011	IUCE main effect, p=0.014	IUCE main effect, p=0.044	IUCE main effect, p=0.044
	Model F (2, 131) = 4.65, p= 0.011	*Model F* (5, 128) = 2.01, p= 0.082	*Model F* (10, 122) = 2.28, p= 0.018	*Model F* (12, 118)= 2.13, p= 0.019
	R^2=0.066	R^2=0.073	R^2=0.157	R^2=0.176
3b.*Narrative Memory* subtest	M (SD)[f]; *p*-value	LSM (SE)[g]; *p*-value	LSM (SE); *p*-value	LSM (SE); *p*-value
Heavier IUCE	9.44 (3.43); 0.646	8.80 (0.72); 0.464	8.02 (0.67); 0.057	8.11 (0.72); 0.087
Lighter IUCE	7.83 (3.33); 0.548	7.62 (0.50); 0.008	7.71 (0.45); 0.003	7.71 (0.47); 0.004
Unexposed	9.08 (3.34)	9.47 (0.44)	9.67 (0.42)	9.69 (0.44)
	IUCE main effect, p=0.079	IUCE main effect, p=0.026	IUCE main effect, p=0.011	IUCE main effect, p=0.014
	Model F (2, 133) = 2.58, p= 0.079	*Model F* (5, 130) = 2.22, p= 0.056	*Model F* (10, 124) = 5.16, p< 0.001	*Model F* (12, 118) = 4.36, p< 0.001
	R^2 = 0.037	R^2=0.079	R^2=0.294	R^2=0.336

*NEPSY= NEPSY: A Developmental Neuropsychological Assessment [71]

[a]Model 1 independent variable: Level of IUCE only

[b]Model 2 independent variables: Level of IUCE plus intrauterine exposure to tobacco, marijuana, and alcohol

[c]Model 3 independent variables: Model 2 variables plus child sex, prorated IQ, caregiver's education, and custody arrangements

[d]Model 4 independent variables (auditory attention): Model 3 variables plus child's birth weight, age at the time of the 9.5 year visit, and violence exposure/victimization

[e]Model 4 independent variables (narrative memory): Model 3 variables plus birth head circumference, current caregiver's marital status, and current caregiver's marijuana use

[f]M (SD) = arithmetic mean (standard deviation)

[g]LSM (SE) = least square mean (standard error), adjusted for all variables in the model