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Intrauterine Cocaine Exposure and Executive Functioning in Middle Childhood

Ruth Rose-Jacobs, Sc.D.^a, Deborah Waber, Ph.D.^b, Marjorie Beeghly, Ph.D.^c, Howard Cabral, Ph.D., MPH^d, Danielle Appugleise, MPH^e, Timothy Heeren, Ph.D.^d, Jodi Marani, M.Ed.^f, and Deborah A. Frank, M.D.^a

^aDepartment of Pediatrics, Boston University School of Medicine and Boston Medical Center, Boston, MA 02118

^bDepartment of Psychiatry, Children's Hospital, Boston, MA 02115

^cDepartment of Pediatrics, Harvard University Medical School, Boston, MA 02115 and Department of Psychology, Wayne State University, Detroit MI 48202

^dDepartment of Biostatistics, Boston University School of Public Health, Boston, MA 02118

^eData Coordinating Center, Boston University School of Public Health, Boston, MA 02118

^f Department of Pediatrics, Boston Medical Center, Boston, MA 02118 (at the time of the study)

1. Introduction

Because cocaine can be a powerful modifier of brain chemistry and structure in chronic adult users [15], [5], the impact of maternal use on the developing and presumably even more vulnerable fetal brain is of great concern. Intrauterine cocaine exposure (IUCE) is thought to affect the circuitry and structure of the developing brain via several possible mechanisms. IUCE may inhibit reuptake of the monoamines dopamine, norepinephrine, and serotonin at the presynaptic junction as well as induce vasoconstriction that could result in nonspecific hypoxic effects on neural growth [52,64]. Although some animal models suggest that IUCE leads to significant postnatal and long-term cognitive and neurodevelopmental sequelae [47], [78], covariate controlled clinical studies in human children have yielded more equivocal findings [25] that may be associated with multiple other pre and post-natal exposures and environmental factors.

The identification of developmental neurocognitive outcomes attributable to IUCE are of clinical and educational importance. Of particular interest are the potential neurocognitive delays or deficits from IUCE that could surface in response to the increased developmental challenges of middle childhood and adolescence, when more complex cognitive processes are required for educational, behavioral, social, and day-to-day functional success and independence [14]. Such effects may be most apparent in aspects of cognition that

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Correspondence should be sent to: Ruth Rose-Jacobs, Sc.D., Department of Pediatrics, Boston University School of Medicine, 91 East Concord Street, Maternity 5106, Boston, MA 02118; rrosejac@bu.edu; fax: (617) 414-7915..

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neuropsychologists refer to as “executive functions” (EF). Fried and Smith [31] summarize EF as “a shorthand, describing a multiple, non-unitary set of cognitive/behavioral abilities critical in effortful, non-routine, goal-oriented situations.” Although there is no consensus on the definition of EF, among the various cognitive functions that have been subsumed under this term are organization, information processing and problem-solving, focused attention, monitoring, updating, working memory, adjusting self-directed responses, inhibition, and cognitive flexibility [59], [88], [4], [63]. Although EF have been associated primarily with the frontal lobes of the cerebral cortex, more contemporary accounts point to networks that recruit diverse regions of brain on a moment to moment basis depending upon the goal. These networks evolve developmentally, becoming more efficient and more focused neuroanatomically with age [22], [3], [74], [31], [88], [14], [30].

1.1 Measurement of Executive Function

The EF construct is broad and can be measured in a variety of ways. Two measures that are well validated and extensively used in clinical and research settings from middle childhood to adulthood as a part of a standard neuropsychological battery of EF are the Stroop Color-Word Test [80] [36] and the Rey-Osterrieth Complex Figure (ROCF) Test [45]. The Stroop test measures cognitive regulation and inhibitory control. The Rey-Osterrieth Complex Figure (ROCF) test measures multiple aspects of neuropsychological functioning including executive skills such as planning, organization, memory as well as perceptual skills, memory and motor function [45] within the context of a visual-perception task.

1.2 Stroop Color-Word Test

During the Stroop Color-Word Test, the participant first is asked to name a series of color patches, then to read color names, and finally to name the ink color of color names printed in conflicting colors (e.g., the word “red” printed in blue ink would be “blue.”) The latter “interference” condition is believed to evaluate the participant's ability to inhibit a prepotent response in favor of a less automatic one. Among other cognitive functions, it requires attention, mental flexibility, and the application of rule governed behavior in the presence of conflicting cues [73], [32], [58]. The Stroop test has been used extensively with children and adolescents [16,36], [21], [48] and adults [20], including adults who have abused substances [69], [37], [23]. Several studies have used the Stroop test to evaluate children with prenatal drug exposure [73], [86], [32], [54]. However, prior studies of IUCE administered the Stroop at a single protocol point and had small samples [86], [54].

In one study primarily addressing prenatal exposures other than cocaine, Richardson et al [73] did not find significant effects of prenatal marijuana and alcohol exposure on the Stroop at age 10, even though learning and memory as evaluated by other measures were affected. Although Fried and Watkinson [33] did identify significant prenatal cigarette and marijuana effects in a factor analysis of several EF outcomes, the construct which contained the Stroop as a single measure was not significant. The researchers suggested that the Stroop as a single outcome for the focus/execute construct may have been too narrow, and therefore may have underestimated drug effects.

1.3 Rey Osterrieth Complex Figure (ROCF)

The Rey Osterrieth Complex Figure (ROCF) [71] is a neuropsychological test that requires the participant to copy a complicated geometric design and then to draw it from memory, immediately and after a delay. As an indicator of executive functioning, compared to the Stroop, the ROCF is thought to measure skills that are more metacognitive in nature such as planning, organization and ability to deploy attention effectively. It also reflects aspects of perceptual organization, motor skills and visual memory [13]. The copy condition is thought to reflect primarily perceptual, visuospatial, and organizational skills; the immediate recall to

reflect the amount of information encoded; and the delayed recall to reflect the amount of information stored and retrieved from memory [61]. The organization and accuracy of the reproduction improves with development, with the greatest improvement occurring between ages 5 and 9 years, although there is continuing improvement through at least 14 years of age [84], [44]. The ROCF has been used with adolescents and adults to identify EF differences between those who have and have not abused substances [81], [10], [5], [83]. However, to our knowledge, the ROCF has not yet been used to evaluate children with and without IUCE.

Several scoring systems exist for quantifying the productions of adults and/or children on the ROCF; however, the Developmental Scoring System (DSS) is particularly sensitive to developmental changes in children [44], [84]. The DSS scoring system has been used to discriminate children suspected of having learning and/or neurological impairments related to many diagnoses including cardiac problems, low birth weight, idiopathic learning disorders, and leukemia [12], [44], [34], [13]. However, the DSS previously has not been used to evaluate children with IUCE.

1.4 IUCE, Neurocognition, and Executive Functions

Regulatory functions that can be foundational for cognitive development do not newly emerge in childhood, but evolve from birth [68], [42], [43]. Early perturbations of regulatory functions induced by IUCE could become elaborated later in life as differences in more complex executive capacities. In fact, during the newborn period, IUCE has been associated with less optimal state regulation, arousal and attention [82], [51], [18], [53]). Heffelfinger, using a visual attention paradigm, identified impairments in the cocaine exposed as compared to the unexposed group among a small sample of children 14 to 60 months of age [38].

Although most studies of IUCE among preschool aged children have not reported deficits in global IQ [29], [40], [79], Singer and Minnes [79], did report modest IUCE-related decrements in scores on specific subtests, reflecting visual-spatial skill, general knowledge, and arithmetic. Richardson [72] found lower scores on the global Stanford-Binet IQ Composite at 3 years of age and poorer short term memory among children whose mothers reported frequent cocaine use during the first trimester. Additionally, examiners masked to exposure status rated the exposed children as less focused and more restless during testing than their unexposed peers. Bandstra and Morrow [8] noted poorer sustained attention in 3, 5, and 7 year old children with IUCE compared to children in the control group. In contrast, Noland and Singer [63] did not find either IUCE or intrauterine marijuana exposure to be associated with performance on a finger tapping inhibition task among 4 year olds.

Neurocognitive studies carried out in middle childhood document fairly consistently a pattern of subtle compromise of cognitive and executive skills associated with IUCE, more prominent in narrow-band than global outcome measures [41]. Morrow and Culbertson [60] reported that the 7 year olds with IUCE were 2.8 times more likely to show learning disabilities, as identified by ability-achievement discrepancies, than controls, even though the IQ and achievement scores of exposed children were not significantly lower than those of their unexposed peers. Schroder and Snyder [77] reported that prenatally exposed 8 to 9 year-olds had slower visual motor speed and poorer delayed recall during timed assessments with the Groton Maze Learning Tests compared to unexposed children. Savage and Brodsky [75], using the Gordon Diagnostic System (a visual continuous performance test measuring impulsivity and sustained attention); the Trailmaking (a measure of planning and set shifting); and Auditory Attention subtests of the Haistead-Reitian Battery, to 10-year-old children from economically impoverished backgrounds who all achieved poor scores relative to published norms. However, the IUCE group made more Errors of Commission on the most difficult of the Gordon tasks, an indicator of mildly compromised attention and impulsivity.

In another study of 10-year-olds with and without IUCE, EF were evaluated neuropsychologically with the Stroop Color-Word Test, a measure of verbal inhibitory control, and the Trailmaking Test [86]. This study linked the above behavioral outcomes to neuroanatomical structure using diffusion tensor imaging (DTI), an MRI imaging technique that evaluates white matter integrity in the frontal callosal and projection fibres [86]. The children with IUCE exhibited less mature development of frontal white matter pathways, performed more slowly on the Trailmaking test and tended to have poorer scores on the Stroop Interference condition than the children who had not been prenatally exposed. Although the DTI findings were related to other prenatal drug exposures as well, it is noteworthy that the children's performance on the EF measures also was systematically related to indices of white matter integrity. In a similar kind of study, Mayes [54] reported that 7-9 year olds with IUCE who performed a Stroop task while event-related potentials (ERP) were recorded took longer to process the stimuli and demonstrated more diverse cortical involvement than the unexposed children, suggesting that the networks were less well specialized. Interpretation of these findings relative to IUCE is limited, however, by the inability of these investigators to control for other prenatal drug exposures given the relatively small sample size.

1.5 Prenatal Exposures and Other Factors that Complicate Measurement of Outcomes in Children with IUCE

Since women who abuse cocaine often abuse other substances, it is important in studies of IUCE to control for other exposures, including alcohol [73], [76], [70], [46], [19], marijuana [49], [86], [73], and tobacco [33] as these can also adversely affect development. In the study by Noland et al [63], four-year-olds who had been exposed prenatally to alcohol performed more poorly on a tapping inhibition task than those who had not been alcohol exposed. In another study, a low-social-risk middle class sample of children ages 9-13 who had been exposed prenatally to marijuana performed more poorly on EF tasks such as sustained attention, problem solving, and analytical skills associated with visual integration, but IQ was not affected [30]. In contrast, children who were prenatally exposed to cigarettes had lower IQs, and poorer impulse control and basic visual-perceptual abilities than their peers who were not exposed prenatally to cigarettes [30]. Methodological differences between studies can also influence outcomes. These may include subject characteristics, demographics, and enrollment criteria; the specific covariates controlled in the analyses; the unknown purity and varying routes of administration and timing of use of the illegal drug during pregnancy; as well as the specific developmental outcomes tested [26], [72]. When evaluating potential IUCE effects, other factors such as, gender, IQ, and maternal education which influence cognitive outcomes of children in general must be addressed either by subject selection or statistical control [7], [56], [27], [51]. Lower birth weight and shorter gestational age have been consistently noted as correlates of IUCE (and of intrauterine exposure to other substances such as tobacco) and must be considered as potential confounds, mediators, or moderators [27]. Moreover, the significant impact of adverse environmental factors associated with poverty in urban areas (e.g. exposure to violence or environmental exposure to lead and other toxins), on the development of both exposed and unexposed children, may lead to misattribution of environmental effects to IUCE unless these factors are statistically controlled when possible [6].

1.6 Purpose

The purpose of this longitudinal study is to evaluate whether the level of IUCE or the interaction between IUCE and contextual variables is related to components of EF as assessed with the Stroop Color and Word Test [36,80] and the Rey Osterrieth Complex Figure (ROCF) [71] in children during middle childhood between the 9.5 and 11 year testing points. Although this age interval is relatively brief, the longitudinal model provides the opportunity to examine whether differences are stable between the two ages, emerge more prominently, or diminish with age.

2. Methods

2.1 Data Sample

The participants were part of a prospective longitudinal study evaluating the effects of level of IUCE on children's growth and development from birth to 11 years of age. All study children were born at Boston City Hospital (now Boston Medical Center) and were from low-income, urban backgrounds. The Human Studies Committees of Boston City Hospital and Boston University School of Medicine approved the study. All birth mothers or other primary caregivers gave written informed consent. Beginning at the 8.5-year visit, the children themselves also provided written assent. In addition, a Certificate of Confidentiality was obtained from the federal government to protect participants from having research data subpoenaed. After each study visit, the caregiver was given \$50 store vouchers for completion of the interview and bringing their child in for the developmental assessment. In addition the child received an age appropriate gift.

Infant-caregiver dyads were recruited daily for the longitudinal study from the postpartum unit of Boston Medical Center (previously Boston City Hospital) from October 1990 to March 1993 if they met the following inclusion criteria: infant gestational age ≥ 36 weeks, no obvious major congenital malformations, no requirement for neonatal intensive (NICU) care, no diagnosis of fetal alcohol syndrome in the neonatal record, and no indication (either by neonatal or maternal urine toxic screen or meconium assay or by history in medical record) of prenatal exposure to illegal opiates, methadone, amphetamines, phencyclidine, barbiturates, or hallucinogens, and no history of HIV seropositivity noted in the infant's or mother's the medical record. In addition, mothers had to be at least 18 years old and fluent in English. These criteria excluded subjects with known major risk factors (e.g., premature birth) that might confound any specific effects of IUCE on child outcomes. English fluency was required because the neuropsychological measures planned for this cohort at older ages were not standardized for non-English speakers. Further details about recruitment procedures and sample characteristics are reported elsewhere [28].

2.2 Intrauterine Cocaine Exposure Classification

Research staff interviewed study mothers at intake during the postpartum period about their pregnancy and lifetime use of cocaine, alcohol, marijuana, cigarettes, and other illicit drugs using an adaptation of the fifth edition of the Addiction Severity Index (ASI) [55]. Prenatal cocaine use was determined by a combination of biological markers and positive self report. At least one biological marker (maternal or infant urine, or infant meconium) was obtained for each recruited dyad to confirm maternal self-reported exposure status. Urine samples were analyzed for benzoylecgonine, opiates, amphetamines, benzodiazepines and cannabinoids by radioimmunoassay using commercial kits (Abuscreen RIA, Roche Diagnostics Systems, Inc., Montclair, N.J.). We also sought to collect meconium specimens from all enrolled infants for analysis by radioimmunoassay for the presence of benzoylecgonine, opiates, amphetamines, benzodiazepines and cannabinoids, using a modification of Ostrea's method [65].

Children were classified as cocaine exposed if there had been evidence of maternal use during pregnancy by positive maternal self-report, urine assay, or meconium assay. Further, based on composite information derived from maternal self-report and/or the meconium assays, subjects exposed to cocaine were classified as either heavier or lighter exposed. "Heavier" use was defined a priori among users as the top quartile of days of mother's self-reported use during the entire pregnancy and/or the top quartile of concentration for cocaine metabolites in the infant's meconium. This procedure was used because women are more likely to under-report than over-report illicit substance use during pregnancy [66] and because not all infants with IUCE have positive meconium assays [50].

The mean days of maternal self-reported cocaine use during pregnancy in this cohort was 20.6 days (range = 0–264) and mothers reporting 61 or more days of cocaine use during pregnancy fell into the top quartile and were considered “heavier” users. The mean meconium concentration was 1143 ng of benzoylecognine per gram of meconium (range = 0 to 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” group. All other IUCE was classified as “Lighter”. The children classified as unexposed were those for whom self-report by the mother was negative and there were confirmatory negative findings on the biologic assays. This conservative classification system was used to assure that any outcome differences between the Heavier exposed and other groups were not due to inflation of the Heavier group based on urine assays alone and because 18 of 141 (13%) of the infants in the present sample (14% in the larger study) had no meconium assay.

This ordinal classification scheme is similar to that used by other investigators of prenatal substance exposure [2,41,79]. Prior research in the present cohort indicated that level of cocaine exposure defined this way significantly was related in a dose-related manner to lower birth weight z-scores (adjusted for gestational age and gender) [26], neonatal ultrasound findings [28], and less optimal patterns of newborn neurobehavior [82]. For consistency with previous work in this cohort, an ordinal IUCE variable (Unexposed, Lighter, Heavier) as defined above was used for initial analyses and then if inspection of the data warranted, a dichotomous IUCE variable (Lighter and Unexposed versus Heavier exposed) was used as the next step of the statistical analyses [82].

2.3 Design

The children were evaluated at multiple time points between their birth and 11 years [27], [29,82], [11]. Data included in the present report were collected as part of the protocol points when the children were 9.5 and 11 years of age. At each protocol point primary caregivers brought the children to the Infant and Child Development Laboratory in the General Clinical Research Center at Boston Medical Center. During each visit caregivers were interviewed by a trained research interviewer on topics including demographics, recent substance use, and the developmental and caregiving environments. At the same protocol points, the children were tested by different individuals who were trained developmental examiners and masked to children's IUCE status, background variables, caregivers' responses on the interviews, and scores on prior developmental assessments.

2.4 Measures

At the 9.5 and 11 year protocol points the child protocols included the administration of the Stroop [80] Color-Word Test and the Rey Osterrieth Complex Figure (ROCF) [71].

2.4.1 Stroop Color-Word Test—The Stroop task has three parts and during each part the child was asked to read stimuli from a card as quickly as possible without making mistakes, with a 45 second time limit. Each card displays a total of 100 stimuli in five columns of 20 items each, with the stimuli arrayed randomly. The first card, Word, displays the color names (green, blue and red) written in black ink. The second card, Color, displays color patches of four X's in one of the three ink colors, and the child is to name the color. The third card, Interference, displays color names printed in a conflicting ink color and requires that the child name the ink color but ignore the word. If a child made an error and did not self-correct, the examiner said “no” and asked the child to make the correction.

Each condition was scored in terms of the number of items correctly read in 45 seconds. The standardized Interference T Score was calculated based on published norms [36]. Higher Interference T Scores are less optimal.

2.4.2 Rey Osterrieth Complex Figure (ROCF)—The child was asked first to copy the model of the visually complex ROCF printed figure onto a blank sheet of paper (copy condition). Colored markers were used and changed after a specified time period in order to capture the order in which the design was drawn. After the copy production was completed, the model and the child's copy were removed by the examiner and the child was asked to draw the same figure onto another blank sheet of paper, this time without the model (immediate recall). After 15 minutes of non-related testing, the child again was asked to draw the figure onto a blank sheet of paper without the model (delayed recall).

The Developmental Scoring System (DSS) was used to score the copy, immediate and delayed recall productions [13]. This system employs objective criteria to evaluate specific components of the figure; Organization, Accuracy, Style, and Errors [13]. The Organization score, the primary scoring outcome, is intended to capture the goodness of the construction of the overall figure and main components of the figure [84]. Accuracy reflects the number of structural or incidental elements of the figure that are reproduced, regardless of the organization of the figure. Errors refers to distortions and are usually a rare event, generally occurring two to three times per protocol, and when more frequent at any age may be concerning [84]. Errors are a tally of the events of rotation, misplacement, perseveration, and conflation of elements [84]. A mature ROCF drawing usually has a higher Organization score and fewer Errors although a scant drawing could have a low Organization score and fewer Errors because of a minimal drawing production. ROCF-DSS reliability has been reported by the test authors to range from .91 to .96 with reliability of .95 for the copy, and .94 for recall for organization [13]. To optimize reliability and guard against “drift” over time in application of the ROCF-DSS scoring system to the complex figures, two examiners (masked to cocaine status) were initially trained by one of the test authors (DW) to use the scoring system. This was followed by independent double scoring of the same protocol by the two examiners until they were consistent with the scores reconciled by the study author who also was masked to cocaine status. After this initial training period, the two examiners double scored and reconciled any differences on the first ten sets of study protocols which also were independently scored by DW. This process was repeated midway through the testing, on at least every tenth protocol, and then on the last five protocols. In each case, any differences in scoring were discussed and reconciled to ensure that the scorers continued to use the correct scoring procedures.

2.5 Control Variables

A trained interviewer research assistant who was not one of the research assistants conducting the developmental assessments of the children, and was unaware of those assessments, interviewed the care giver and elicited demographic variables, caregiver's status (birth mother, kin caregiver, or unrelated caregiver), and caregiver's recent use of licit and illicit substances at the time of each child's assessment.

Potential candidate control variables were selected *a priori* on the basis of previous literature, earlier findings in this cohort, and on theoretical grounds. Cocaine use rarely occurs in the absence of concomitant use of one or more of other psychoactive substances. Thus, possible IUCE effects might be masked by other exposures or the effects of other drugs misattributed to cocaine exposure. Prenatal exposures were ascertained during the neonatal maternal interview in addition to the meconium and mother/neonatal urine assays previously described. Therefore, we *a priori* planned to include prenatal use of alcohol (mother's self reported average daily volume of alcohol in drinks per day, a commonly used standardized measure of consumption), marijuana (“yes” or “no”, any prenatal marijuana use based on positive results of urine assay, meconium assay, or maternal self-report) and cigarettes (self-reported average number of cigarettes per day during pregnancy) in the list of control variables [50]. The natural log of the prenatal alcohol as well as cigarettes was used to stabilize the variances of these

measures. Other candidate covariates included: child age at exam, gender, and current and/or prior prorated IQ as measured by the Wechsler Intelligence Scale for Children, 3rd. ed. (WISC-III) administered at the 8.5 and 11 year protocols [87], z-score of birth weight adjusted for gestational age and gender [17], birth mother's education, birth mother's self-identified African American/Caribbean ethnicity versus other, current category of caregiver (birth mother, kinship caregiver, or unrelated foster or adoptive parent), and exposure of the child to violence as measured by the Violence Exposure Scale for Children-Revised (VEX-R)[24]. Current category of caregiver variable is a partial proxy for home environment. The VEX-R is a 21 item, 4-point Likert self-report scale using cartoon pictures that is intended to examine a child's exposure to violence as witness and victim ranging from mild (yell, push, spanking) to severe (threaten with a weapon, shoot, stab). The VEX-R was administered at 8.5, 9.5 and 11 year protocols. The distribution of VEX-R scores was ranked at each time point and then subdivided into 4 groups of approximately equal size. The maximum of these quartile variables was then taken up to the time of the EF measurement and used as a time-dependent covariate in the analyses. The ROCF, unlike the Stroop, had three administrated conditions, and therefore condition of administration was a within subject variable in the statistical analyses. Caregivers' postpartum use of alcohol, cigarettes (by self-report), marijuana, and cocaine (by self report or assay) were sufficiently correlated with prenatal substance use that variables representing postnatal use could not be included in the analysis model (analyses available from first author on request).

2.6 Statistical Analyses

We approached our data analyses in stages. First, we performed univariate analyses to examine distributional characteristics using descriptive statistics, calculated means and standard deviation, constructed histograms for continuous variables (e.g. Stroop Interference, ROCF Organization), and reported frequency counts and percentages for categorical variables (e.g. prenatal marijuana exposure and ethnicity). Next, we examined bivariate relationships unadjusted for potential confounding variables between IUCE, our primary independent variable, (using two dummy variables, Lighter versus Unexposed and Heavier versus Unexposed) and EF outcomes using linear models estimated via GEE (generalized estimating equations) [89]. These models are appropriate for the analysis of longitudinal data taking into account the correlation of the data within subjects and examining the within-subjects factors, exam condition (for the ROCF) and age-at-exam (for both ROCF and Stroop, 9.5 and 11 years for each protocol). The models were then extended to adjust for the covariates of theoretical interest described above if a variable altered the estimates of the associations with cocaine by 10% or more [57]. While this approach does not identify which of all measured variables best predict outcome, it is thought to yield the most valid estimate of the impact of the exposure of interest in a behavioral teratology study such as this one [57]. When these criteria were applied to all the previously listed candidate covariate variables, including time dependent exposure to violence measured by the VEX- R [24], variables retained in the Stroop adjusted model included age, gender, other prenatal drug exposures (alcohol, marijuana, and cigarettes) and birth weight z-score. The variables retained in the covariate-adjusted model for the ROCF included age, task condition, prorated IQ, other prenatal drug exposures (alcohol, marijuana, and cigarettes) and birth weight z-score. To address the question of differential longitudinal effect of the IUCE groups on executive function, we tested the interaction of IUCE with age for each outcome. In each model we also checked the interactions of IUCE with each covariate on the outcome variables, using a significance level of 0.05. Where interactions were shown not to be statistically significant, we dropped the interaction terms from the model. Given that our analyses showed similar results for the Lighter and Unexposed IUCE groups, we performed *post hoc* contrasts of Heavier versus Lighter/Unexposed, as we did in prior studies based on infant assessments in this same cohort [82]. In addition to presenting differences in mean scale scores between groups, we computed effect sizes (ES) equal to the difference between group

means (adjusted if estimated from multiple regression models) divided by the pooled standard deviation of the scores for the two groups.

3. Results

3.1 Sample Retention

One hundred forty-one of the study's original 252 children were retained to school age and completed at least one Stroop and one ROCF test across the two ages. We examined the potential retention bias by comparing those who provided data in the 9.5 and 11 year protocols (n=141) to those in the original birth cohort who did not provide data during this middle childhood period (n=111). The evaluated and not evaluated groups did not differ substantively or in terms of statistical significance on level of IUCE (p=0.45) or on key covariates including prenatal exposures to cigarettes (p=0.80), alcohol (p=0.60), or marijuana (p=0.66); birth weight (p=0.49); gestational age (p=0.24); infant gender (p=0.45); maternal education (p=0.39), age (p=0.31) or primiparity (p=0.98) at delivery; public/private health insurance payment status (p=0.64); and African-American/Caribbean ethnicity (p=0.14).

Of the 141 in the Stroop/ ROCF sample, 113 completed the Stroop and 106 completed the ROCF at each of the two ages; 28 completed the Stroop at one point (16 at 9.5 years and 12 at 11 years) and 35 children completed the ROCF at one point (15 at 9.5 years and 20 at 11 years). There were no significant differences ($p>0.05$) between those who contributed one versus two Stroop tests for: 3-level IUCE, gender, prenatal exposure to marijuana or cigarettes. However there was a significant difference ($p=0.01$) for prenatal alcohol exposure. Those with one Stroop test had the prenatal exposure of 0.02 log of average daily volume of alcohol while those who completed the Stroop at both ages had a higher prenatal exposure of 0.14 log of average daily volume of alcohol. There were no significant differences at the 0.05 level between those who contributed one versus two ROCF tests for 3-level IUCE, gender, prenatal marijuana, cigarettes, or alcohol.

3.2 Sample Characteristics

Characteristics of birth mothers and children by the three cocaine exposure groups on the 141 subjects who completed at least one of the EF assessments are presented in Table 1. There were significant differences ($p<0.05$) across the IUCE groups on the following variables: prenatal exposure to cigarettes, alcohol, marijuana, childhood caregiver (both at ages 9.5 and 11 years), birth weight z-score, and maximum sample quartile of VEX-R up to 9.5 years. There was a trend ($p=0.06$) of differences across exposure groups for the maximum sample quartile of VEX-R up to 11 years. There were no significant differences across cocaine exposure groups by birth mother's ethnicity, birth mother's education, child's gender, ages at testing, or WISC-III prorated IQ scores.

3.3 Stroop Color-Word Interference: Unadjusted Analyses

Unadjusted means and standard deviations for the Stroop Interference t-score at each age by IUCE group are presented in Table 2. The means cluster around the standardization population mean of 50. There were no significant group differences in the proportion of children with Interference scores one standard deviation (SD=10) above or below the population mean ($p=0.92$). In unadjusted analyses with IUCE as a three level predictor variable the Interference means were not significantly different by IUCE group at 9.5 years (effects size (ES) =.29; $p=0.43$) although there was a small to moderate effects size. At 11 years of age there was a significant difference across the three IUCE groups and a moderate to large effect size (ES=.68; $p=0.001$), reflecting an improved score in the control group.

3.4 Stroop Color-Word Interference: Adjusted Analyses

Results for the covariate controlled regressions for the Stroop Interference scores are presented in Table 3. For these analyses, data were combined across ages and the 3-level IUCE variable was the independent variable. There were no significant effects of IUCE status when scores were adjusted for children's age in years at the time of testing and gender or after additionally adjusting for prenatal alcohol, marijuana, and cigarette exposure, and birth weight z-score. However, in the two level post-hoc analyses the Heavier exposed compared with the Lighter/Unexposed group exhibited poorer Interference scores whether controlled for age and gender [Difference of means = 3.83 (1.51), ES=.46, $p=0.01$] or after adding the additional control variables of prenatal drug exposures, and birth weight [Difference of means = 3.97 (1.85), ES= .46, $p=0.03$]. In both analyses there were moderate to large effects sizes. There were no significant interactions between IUCE and the covariates in any of the above analyses. When the analyses were restricted to the 113 children who completed the Stroop at both ages, the effects sizes for the analyses for the restricted sample and the larger sample of 141 were similar.

3.5 Rey Osterrieth Complex Figure: Unadjusted Analyses

Given that there were three conditions of the ROCF at each of the two ages, 747 drawings (or observations) were included in the dataset. The unadjusted ROCF means and standard deviations at each age and for each ROCF condition by IUCE group are presented in Table 4. None of the unadjusted variables were significantly different by IUCE group although at 11 years of age there was a trend for the mean Organization scores for the Immediate Recall ($p=0.06$) and Delayed Recall ($p=0.11$) conditions to differ across exposure groups.

3.6 Rey Osterrieth Complex Figure Outcomes: Adjusted for Covariates

Covariate-controlled regression results for the ROCF are presented in Table 5, where data are collapsed across age and task condition, and 3-level IUCE status was the independent variable. There were no significant effects of IUCE groups with adjustment for age in years, condition, and prorated IQ or after additional control for prenatal alcohol, marijuana, cigarettes, and birth weight. Also, there were no significant interactions between IUCE status and any of the covariates, including age. In the two level post-hoc contrasts with age, task condition, and prorated IQ controlled, the Heavier IUCE group had significantly poorer Organization scores [difference in means = $-.93$ (0.39), ES= $-.32$, $p=0.02$] and tended to have fewer Total Errors [Difference in means = $-.65$ (0.34), ES= $-.23$, $p=0.07$] than the Lighter/Unexposed group. With the addition of the other prenatal drug exposures and birth weight to the model, the two level IUCE post-hoc analyses identified only a trend for the Heavier group to have poorer scores on Organization [Difference in means = $-.62$ (0.43), ES= $-.23$, $p=0.15$] and significantly fewer Total Errors [Difference of means = $-.88$ (0.35), ES= $-.32$, $p=0.01$] than the Lighter/Unexposed group. When the analyses were restricted to the 106 children who completed the ROCF at both ages, the effects sizes for the analyses for the restricted sample and the larger of 141 sample were similar.

4. Discussion

Results of this study demonstrated relatively subtle differences in laboratory measures of EF during middle childhood associated with IUCE in covariate controlled analyses. These findings were present even in the absence of major cognitive differences in the same cohort as measured by standardized instruments in infancy [27] and early childhood [29]. The differences reached formal criteria for statistical significance on the Stroop test, a measure of on-line regulation and inhibition, but showed only a non-significant trend on the Rey-Osterrieth Complex Figure test, a complex task that, unlike the Stroop requires substantial planning, organization and integration.

4.1 Stroop Color-Word Test

As hypothesized, even when the analyses were controlled for age, gender, other drug exposures and birth weight z-score, children in the Heavier IUCE group demonstrated poorer Interference scores on the Stroop task than children in the Lighter/Unexposed group. The statistical differences were present even though the mean Interference scores in each of the three exposure groups were within the normal range based on the normative sample.

Our finding is consistent with prior research which suggested that IUCE could have had an impact on the development of white matter tracts as a potential source of the difference on Stroop performance in their cocaine exposed and unexposed groups of children [86]. Our finding is also supported by Mayes' [54] report that children who had been exposed to cocaine engaged more diverse brain areas and needed more processing time on a Stroop task than the unexposed group. Importantly, however, because of the latter study's small sample size, other prenatal drug exposures could not be controlled, and it is therefore not possible to attribute their finding specifically to IUCE.

The unadjusted Stroop Interference means shed light on the results of our multivariate analyses. The mean T scores were all close to the population mean of 50 but showed somewhat different patterns across IUCE groups and ages. The unadjusted means for Interference differed statistically by IUCE group with a large effect size at 11 years of age in a dose response pattern. At 9 years of age, there was a similar pattern, although not statistically significant. Interestingly, the mean scores of the Unexposed group improved slightly with age whereas the mean score of the Heavier group (and to a lesser degree, the Lighter exposed group) worsened with age. In addition, group standard deviations of the Stroop Interference scores decreased with age in each IUCE level. It is plausible that the children's performance also became more reliable at the older age allowing an underlying difference to emerge more reliably and therefore be statistically detectable. Whether these group differences are stable and become more pronounced with age or reflect transient variability in maturation of EF performance will be clarified by the results of our planned follow-up during these children's adolescence.

4.2 Rey Osterrieth Complex Figure

Contrary to our hypothesis, although children in the Heavier IUCE group demonstrated poorer Organization on the ROCF than children in the Lighter/Unexposed group when the analyses were controlled for age, condition, and prorated IQ, the effect was not robust when additionally controlled for alcohol, marijuana, cigarettes, and birth weight Z score. Therefore it appears that the unadjusted findings cannot be attributable specifically to IUCE.

What is most striking about the findings, however, is how poorly all the children in the sample, those with or without prenatal exposures, performed on this particular task (as contrasted with the Stroop, on which their mean performance was consistent with the population mean). The mean Organization scores in our sample were comparable to those of 7 to 8-year olds, based on the normative sample which included children who came from a middle to lower-middle-class school district in the northeastern United States [13]. While the Stroop manual did not describe the socio-economic status of the normative sample of children for that assessment, it is very likely that the sample was also from a middle-class background [36]. Unlike the Stroop test, which involved relatively rote information processing abilities, the ROCF requires the ability to manage complexity and to integrate multiple cues. The adverse circumstances associated with poverty, within which all these children were being raised, appear to have had a disproportionate impact on tasks that require higher order integration and organization [85]. We also tested the variable of exposure to violence however, this variable did not statistically change the relationship of IUCE to the Stroop or the ROCF. Within the context of this study, a more subtle variation in performance related to IUCE may have been quite difficult to detect.

However, until the present sample is longitudinally tested at older ages with more than the current two ROCF data points, the developmental trajectories of the cocaine exposed and unexposed groups cannot yet be evaluated.

Of note, in the unadjusted analyses (Table 4) although not statistically significant, the Heavier exposed group had lower (and therefore poorer) mean raw scores for Organization on the Immediate and Delayed Recall conditions at 11 years than they did at 9 years of age even though the Copy condition mean scores across those ages increased. Similar results emerged when we limited the analyses to those children who were given the ROCF test at both 9 and 11 years. Lower Immediate and Delayed Recall Organization scores in the Heavier group may indicate initial difficulties in encoding the visual material, therefore limiting the information stored and retrieved from memory [13]. Our finding of significant Organization differences in the post hoc comparison of Heavier exposed versus Lighter/Unexposed when the model was controlled only for age in years, condition, and prorated IQ became a non-significant statistical trend when the other prenatal drug exposures and birth weight z-score were added indicates that the initial differences were not completely attributable to IUCE. The modified relationship of Heavier cocaine exposure to the ROCF in the different covariate controlled models underscores the importance of covariate control, particularly with other prenatal drug exposures, which may attenuate the relationship of interest [25]. While we reported that the Heavier exposed group had significantly fewer errors than the Lighter/Unexposed group in the covariate controlled analyses, this difference disappeared when the number of errors was adjusted for the number of parts drawn (error ratio), indicating that the Heavier exposed children may have made fewer errors because they drew fewer parts of the figure used as a model.

4.3 Importance of study

The Stroop test has been linked to sustained visual attention and processing and modulating task-relevant and task irrelevant information [1], [9], abilities that are important in daily functioning. Therefore, beyond middle childhood, children with IUCE may be at greater academic, psychosocial and behavioral risk due to neurocognitive issues related to EF [62], [35], [39]. Our present analyses are especially interesting because, while the Heavier cocaine exposed children performed more poorly than the Lighter and Unexposed children on some measures of EF during middle childhood, a similar pattern of differences did not emerge on standardized assessments of global functioning in this sample during infancy [27], at 4 years of age [29], as well as on the WISC- III given in the current assessment. The emergence of these subtle IUCE effects on EF at this point in development suggests the possibility of neurocognitive “sleeping effects” of IUCE which become more apparent with the greater functional and cognitive demands of late middle childhood and preadolescence. Since our project has continued to follow these children into adolescence, we will be able to address the potential longer term significance of these relatively subtle findings.

4.4 Limitations

There are important limitations to this study. First, our study was intended to identify group differences between the three IUCE groups with respect to cognitive and behavioral outcomes, rather than the mechanisms behind the differences. Studies attempting to identify mechanisms usually require technology such as fMRI and ERP. By necessity, those types of studies have smaller sample sizes than ours, and can control for fewer variables. Both types of studies are important in identifying the differences and mechanisms associated with IUCE. Second, without the simultaneous testing of visual-perceptual abilities that do not include motor responses other than pointing, the specific role of visual-perceptual abilities in our ROCF results is unknown. Moreover, despite our diligent attempts to assure reliability and validity in our scoring of the ROCFs, it remains possible, albeit unlikely, that the results for that measure

reflect some undetected variability in scoring. Third, our study does not address the role of attention as a factor underlying the poorer performance of children on both the ROCF and the Stroop. Although attention is a factor of both assessments, the Stroop and ROCF may require different aspects of attention given that each has a unique cognitive load and conditions [67]. Fourth, our study covers only two middle childhood protocol points. Until the longer term longitudinal data become available it is not clear whether the IUCE group differences observed in this study are due to immaturity, delays in development, or potentially persistent deficits. Additionally other environmental factors, particularly early exposure to lead, might have influenced our results. Lead exposure was considered however, since this was a research rather than clinical study, those blood level values from medical record reviews were available only for a part of the sample that received medical care at a specific clinic and were non-representative of the sample as a whole. Future studies of executive function and prenatal cocaine exposure should include prospective ascertainment of lead exposure levels in the study design.

4.5 Conclusions

The results of this study indicate that Heavier IUCE is associated with mild compromise on selective areas of neurocognitive development during middle childhood, specifically cognitive regulation as measured on the Stroop Color Word Test. This study underscores the importance of longitudinal assessment into adolescence of higher-level cognitive functions in children with IUCE and other potential neurobehavioral teratogens, particularly since it may only be the later emerging aspects of EF that show exposure effects. Longitudinal follow up of these subjects and similar cohorts will determine whether the present findings persist at later ages and provide a better appreciation of their functional significance in these children's every day lives. Further research should address the relationship of EF measures and functional academic, psychosocial, and other risk outcomes in children who were prenatally exposed to cocaine and other substances. Lastly, this study again underscores the importance of covariate control of other prenatal exposures in IUCE studies.

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Table 1

Sample characteristics by three level intrauterine cocaine exposure (N=141)

Sample characteristics by three level intrauterine cocaine exposure (N=141)				
Subject characteristics	Intrauterine cocaine exposure			
	Unexposed (n = 68)	Lighter Exposed (n = 48)	Heavier Exposed (n = 25)	P
Birth mother characteristics				
Ethnicity: African American/African Caribbean	91%	85%	92%	0.67 [*]
Maternal education at child's delivery (years) ^{**}	11.56 (1.43)	11.65 (1.38)	11.36 (0.99)	0.69 [†]
Log average prenatal cigarettes during pregnancy ^{**}	0.54 (1.07)	1.42 (1.14)	2.01 (1.10)	<.0001 [†]
Log average daily volume alcohol (last 30 days pregnancy) ^{**}	0.001 (0.008)	0.14 (0.40)	0.36 (0.72)	0.0003 [†]
Marijuana use during pregnancy (any, by assay or positive self-report positive)	10%	31%	36%	0.004 [*]
Caregiver category at 9.5 years				
Birth mother	98%	61%	48%	< 0.0001 [*]
Kinship Caregiver	0	24	35	
Non-kinship Caregiver	2	15	17	
Caregiver category at 11 years				
Birth mother	95%	63%	58%	< 0.0001 [*]
Kinship Caregiver	3	17	32	
Non-kinship Caregiver	2	20	10	
Child characteristics				
Birth weight (g) ^{**}	3353.40 (523.55)	2994.67 (402.90)	2885.28 (381.78)	<0.0001 [†]
Gender – Male	53%	48%	52%	0.86 [*]
Age (years) at 9.5 year protocol (n = 130) ^{**}	10.0 (0.5)	9.8 (0.3)	9.8 (0.3)	0.15 [†]
Age (years) at 11 year protocol (n= 121) ^{**}	11.1 (0.7)	11.1 (1.0)	11.1 (0.7)	0.97 [†]
WISC-III prorated IQ at 8.5 years (n=127) ^{**}	88.0 (15.1)	86.9 (16.9)	88.4 (15.7)	0.91 [†]
WISC-III prorated IQ at 11 years (n=119) ^{**}	86.2 (15.4)	88.6 (18.6)	92.1 (14.9)	0.40 [†]
Maximum sample quartile of VEX-R up to 9.5 years				
1 st	11%	29%	8%	0.01 [*]
2 nd	31	12	13	
3 rd	31	17	46	
4 th	28	43	33	
Maximum sample quartile of VEX-R up to 11 years				
1 st	6%	20%	8%	0.06 [*]
2 nd	24	13	8	
3 rd	37	22	44	
4 th	33	46	40	

^{*} P-value via chi-square test.^{**} Means (S.D.) P-value via one-way ANOVA.[†] P-value via one-way ANOVA

Table 2

Unadjusted means and standard deviations for Stroop Color-Word Interference t score by three-level intrauterine cocaine exposure and age at assessment

Age of assessment	Stroop Color-Word Interference			<i>P</i> value
	Unexposed <i>N</i> = 68	Lighter Exposed <i>n</i> = 48	Heavier Exposed <i>n</i> = 25	
9.5 years mean (<i>s.d.</i>) [*]	50.11 (9.86)	49.24 (10.05)	52.71 (10.27)	0.43
11 years mean (<i>s.d.</i>) ^{**}	47.17 (6.97)	50.80 (6.82)	53.05 (5.62)	0.001

* Unexposed *n*=65, Lighter *n*=42, Heavier *n*=22

** Unexposed *n*=60, Lighter *n*=43, Heavier *n*=22

Table 3

Covariate controlled regression results for Stroop Color-Word Interference T score (data combined across age) by three level and two level intrauterine cocaine exposure

	Three-level cocaine exposure*			Two-level cocaine exposure	
	Unexposed n = 68	Lighter n = 48	Heavier Exposed n = 25	Heavier vs. Lighter/Unexposed	P Value
Covariates					
Age in years and gender	Mean (SE) 48.90 (0.83)	Mean (SE) 49.94 (1.10)	53.25 (1.35) 53.25 (1.35)	Difference of means 3.83 (1.51)	0.01
Age in years, gender, prenatal exposures to alcohol, marijuana, cigarette, and birth weight z score	48.76 (0.96)	50.08 (1.12)	53.39 (1.85)	3.97 (1.85)	0.03

* Partial F test comparing adjusted means across the three IUCE groups, P-value > .05

Table 4

Unadjusted means and standard deviations of Rey Osterrieth Complex Figure (ROCF) variables by task condition, three-level intrauterine cocaine exposure and age at assessment

Age of assessment	ROCF variables and task conditions			P value
	Unexposed <i>n</i> =68	Lighter Exposed <i>n</i> =48	Heavier Exposed <i>N</i> =25	
9.5 year assessment, (<i>n</i>)	66	39	22	
Organizational score				
Copy	4.89 (2.54)	5.13 (2.76)	4.64 (1.99)	0.76
Immediate recall	4.33 (3.32)	4.92 (3.00)	4.32 (3.05)	0.63
Delayed recall	4.72 (3.03)	5.32 (2.66)	4.45 (3.50)	0.50
Structural element score				
Copy	22.63 (3.92)	23.18 (2.86)	21.59 (4.52)	0.29
Immediate recall	17.69 (6.23)	17.00 (6.40)	16.91 (5.76)	0.81
Delayed recall	17.77 (5.63)	18.21 (5.34)	17.68 (5.42)	0.91
Incidental element score				
Copy	35.02 (5.81)	35.10 (4.71)	34.91 (6.35)	0.99
Immediate recall	24.42 (7.44)	22.74 (8.34)	21.55 (5.79)	0.24
Delayed recall	24.48 (7.17)	22.76 (8.07)	23.14 (6.74)	0.48
Error score				
Copy	3.46 (3.07)	3.77 (2.45)	3.18 (2.89)	0.73
Immediate recall	4.40 (2.94)	4.34 (3.18)	3.32 (2.23)	0.30
Delayed recall	5.37 (4.11)	4.82 (3.12)	4.73 (3.59)	0.68
11 year assessment (<i>n</i>)	58	45	19	
Organizational score				
Copy	5.72 (2.73)	5.62 (2.86)	5.06 (2.53)	0.66
Immediate recall	5.26 (3.54)	5.40 (3.21)	3.33 (2.00)	0.06
Delayed recall	5.81 (3.83)	5.47 (3.28)	3.77 (2.64)	0.11
Structural element score				
Copy	23.67 (2.24)	23.49 (2.59)	23.63 (2.09)	0.93
Immediate recall	17.60 (6.32)	18.77 (5.61)	16.42 (5.32)	0.33
Delayed recall	17.30 (6.93)	18.63 (5.74)	18.06 (5.55)	0.58
Incidental element score				
Copy	36.78 (3.84)	35.93 (4.13)	36.53 (4.09)	0.57
Immediate recall	25.22 (8.90)	25.07 (7.90)	25.00 (7.05)	0.99
Delayed recall	25.23 (8.92)	24.77 (8.54)	26.56 (6.55)	0.75
Error score				
Copy	3.16 (2.30)	3.07 (2.54)	2.32 (1.53)	0.37
Immediate recall	3.57 (2.23)	3.86 (2.35)	2.95 (1.90)	0.33
Delayed recall	3.84 (3.36)	3.91 (2.40)	3.94 (1.98)	0.99

Table 5

Covariate controlled regression results for Rey Osterrieth Complex Figure (ROCF) variables (data combined across age and task condition, by three-level intrauterine cocaine exposure)

	ROCF variables	Three-level cocaine exposure*			Two-level cocaine exposure		
		Unexposed $n = 69$	Lighter Exposed $n = 49$	Heavier Exposed $n = 23$	Difference of Means	P Value	
Covariates	Age in years, condition, and prorated IQ	Mean (SE)	Mean (SE)	Mean (SE)			
		5.12 (0.27)	5.18 (0.28)	4.22 (0.34)	-0.93 (0.39)	0.02	
	Structural element	19.50 (0.48)	19.70 (0.50)	18.87 (0.77)	-0.73 (0.84)	0.38	
	Incidental element	28.51 (0.66)	27.50 (0.79)	27.52 (1.02)	-0.48 (1.13)	0.67	
	Total error	4.04 (0.27)	3.98 (0.28)	3.36 (0.30)	-0.65 (0.34)	0.07	
Age in years, condition, prorated IQ, prenatal exposure to alcohol, marijuana, cigarettes, and birth weight Z score	Error Ratio	0.09 (0.01)	0.09 (0.01)	0.08 (0.01)	-0.01 (0.01)	0.36	
	Organization	4.98 (0.28)	5.23 (0.28)	4.49 (0.39)	-0.62 (0.43)	0.15	
	Structural element	19.43 (0.56)	19.76 (0.50)	18.98 (0.83)	-0.61 (0.92)	0.51	
	Incidental element	28.67 (0.75)	27.52 (0.79)	27.18 (1.10)	-0.91 (1.24)	0.46	
	Total error	4.09 (0.25)	3.98 (0.30)	3.16 (0.31)	-0.88 (0.35)	0.01	
	Error ratio	0.09 (0.01)	0.09 (0.01)	0.08 (0.01)	-0.01 (0.01)	0.20	

* Partial F test comparing adjusted means across the three IUCE groups, P -value $> .05$