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Adolescents with and without Gestational Cocaine Exposure: Longitudinal Analysis of Inhibitory Control, Memory and Receptive Language

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Introduction

Preclinical studies of gestational cocaine exposure (GCE) are replete with evidence of changes in brain function at the anatomical, physiological, and behavioral levels, to include effects on developing dopaminergic systems [42,56,83,90,131]. In contrast, human studies of child outcomes have produced less consistent results, with many investigators finding only subtle impairments particularly in tasks of attention, language and memory [1,9,11,47,101,110].

Some of the variability in outcome associated with GCE in humans is undoubtedly attributable to the more complex context in which children develop, compared to the highly controlled environments in animal models. Further it is nearly impossible to control for the myriad of factors that correlate with maternal cocaine use. These factors include SES, concurrent use of other drugs, family mental health history, caregiver characteristics, child exposure to violence as witness or victim, homelessness, and parental separation and loss [19,47,86,91,96,118]. Other reasons for these varied findings may be related both to the measures chosen to assess outcomes in children and the timing of these assessments [6,37].

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Studies of the effects of GCE on language development have shown mixed results. Our group found no GCE effects on language functioning assessed using the Preschool Language Scale at age 2.5 years and the Battelle Developmental Inventory Communication Subscale at ages 3 and 5 years [70,71]. Morrow et al (2004) reported differences of 2 to 3 points on language measures after controlling for important covariates, concluding that their lower standard scores put cocaine exposed children at increased need for clinical interventions [98]. In a trajectories analysis of language performance of children assessed at ages 1, 2, 4, and 6 years, Lewis et al (2007) reported that cocaine exposed children had lower language scores at each age. Average differences between groups in Receptive, Expressive, and Total Language z-scores after controlling for confounding variables were: 0.14, 0.15, and 0.18 [85] which corresponds to 2.1, 2.25, and 2.7 standard score points, respectively. Environmental variables including HOME scores, maternal cognitive functioning and cigarette exposure also were associated with poorer performance. Similarly, Beeghly et al (2006) found that their cohort of low-income, urban children with GCE had lower receptive language scores than unexposed children at age 6 years but not at age 9.5 years [17]. This age difference in GCE effects on language may be due to the contrast between the increasing influence of cumulative environmental factors and the increasingly distal influence of gestational and natal factors.

Because cocaine exposure is associated with alterations in dopamine-rich prefrontal neural systems, functional processes that have been localized to these areas have been examined in exposed children. Prenatal cocaine exposure has been linked to lower levels of inhibitory control [20], a function localized to the anterior cingulate area of the prefrontal cortex (PFC) [5,39,106,112]. Rose-Jacobs et al (2009) identified effects on cocaine-exposed children's ability to inhibit prepotent responses as assessed using the Stroop at ages 5 and 7 years, but in this same cohort scores on a more general measure of executive function showed no cocaine effects [110]. Noland et al (2005) reported effects of prenatal cocaine, tobacco, marijuana on selective attention indicated by higher errors of commission on a picture deletion task administered at age 4 years [101]. Reports from another longitudinal study showed that cocaine-exposed children scored lower than controls on a summary estimate of attention assessed using three measures across ages 3, 5 and 7 years [1,9] and had slightly elevated risk for ADHD according to results of a diagnostic interview [97]. Ackerman et al (2008) reported effects of prenatal cocaine and/or heroin exposure on sustained visual attention assessed using the Connors Continuous Performance test at age 7 years [3]. In the cohort included in the current report, cocaine-exposed subjects made more commission errors on the Distractibility subtest of the Gordon Diagnostic System but had better Delay Task Efficiency Ratios than controls at age 10 years [114]. No GCE effects were observed for each of the 6 remaining measures of attention and impulsivity assessed. These studies suggest that GCE is linked to poorer inhibitory control and sustained attention, yet differences reported often are for only one of many tests administered as found by Savage et al, 2005 [114] and/or effect sizes are relatively small as reported by Morrow et al, 2009 [97].

Imaging studies have shown differences between cocaine-exposed and control subjects in neural characteristics of brain areas that are linked to inhibitory control or attention. Cocaine exposure was related to differences in adjusted volumes in the caudate nucleus [8], more diffuse patterns of activation while performing a task requiring inhibitory control [93], and differences in activation while completing a response inhibition task [116]. In most of these studies no performance differences were observed at the time of evaluation, suggesting that compensatory pathways were developed to ameliorate effects of cocaine exposure on these neural systems.

In studies of more general measures of functioning such as IQ and academic achievement findings are also mixed [22,68,98,118]. In 7 of the 8 studies meeting criteria for inclusion in

a recent review article by Ackerman, no cocaine effects were observed but robust effects of environment were reported [4]. The eighth study showed cocaine exposure effects in the WISC-IV composite for Perceptual Reasoning however no effects were observed for the Verbal Comprehension, Working Memory or Processing Speed Composites or for scores on the Wechsler Individual Achievement Test [118].

It now is well established that GCE has not produced the profound deficits anticipated in the 1980 s and 1990 s, with children described variably as joyless, microcephalic, or unmanageable [15,24,31,52,53,75,92,135]. While welcome, the fact that GCE is not as devastating as predicted in no way negates the need for evaluation for more subtle deficits such as impairments in attention, memory, and language. As is clear in the literature, “subtle deficits” may also have far reaching effects [80,98]. For example, attention deficits that are accepted among family and close friends may be more problematic in the classroom or work place. In the classroom, children with attention deficits have difficulty learning with resultant negative effects on academic performance as they approach adolescence [13]. In the workplace, adults with attention deficits are more likely to be fired, change jobs more often, and earn lower work performance ratings [13]. Since children prenatally exposed to cocaine may exhibit multiple subtle deficits, investigations in maturing youth are merited. Until functional outcomes (i.e., successful transition to adulthood) associated with GCE are evaluated, the clinical significance of these subtle but statistically significant effects remains unknown.

Human brain development is far from complete by late childhood and early adolescence, the oldest age at which children with GCE so far have been studied. There are robust data, to include structural and functional neuroimaging, that show the prefrontal cortex, in particular, undergoes substantial maturational change through adulthood [21,55,107,111,115,123,132]. This is a significant factor in investigations of the effects of GCE given that prefrontal cortex is one of the brain regions most likely to be affected [42,62,84,90]. As such, conclusions regarding the effects of exposure on the human brain cannot be drawn with any finality pending the investigation for such effects on the mature brain. Thus, it is possible that GCE has latent effects on NC outcome that do not manifest until adolescence or young adulthood.

Motivated by the incomplete brain maturation of the oldest subjects so far tested, the possibility of latent or “sleeping” effects as suggested by animal and human research [6,40,54,78,79,81,96,128], as well as effects reported so far by others [2,7,9,17,20,63,76,93,101,109,110,114,117], this report includes assessment of our cohort as they progress through adolescence at ages 12, 14.5 and 17 years. We elected to take a cognitive neuroscience approach to measure NC function in our cohort. Localization of NC systems has been demonstrated in cognitive neuroscience studies that show associations between task performance and activation patterns in imaging or damaged areas in patients with brain lesions. The set of tasks used in this report: 1) evaluated both frontal and nonfrontal function[12]; 2) demonstrated sensitivity to age and IQ[65]; 3) discriminated between middle and low SES subjects[49,99]; and 4) revealed specific relationships between aspects of early childhood experience and the development of specific NC systems[48]. Given this we have confidence that these tasks are psychometrically sensitive for detection of potential differences that may emerge between GCE participants and Controls during later stages of maturation. Data regarding NC functioning of GCE adolescents may identify vulnerabilities in these individuals in the classroom or workplace as they transition into adulthood.

2.0 Methods

2.1. Participants

Our participants were 120, primarily African American youth, approximately half with GCE and half without (Controls). All were recruited at birth from a single inner-city hospital, were born at or near term (≤ 34 weeks), and had 5-minute Apgar scores of at least 5. The children were of low SES as defined by maternal receipt of public medical assistance. None of the children had Fetal Alcohol Syndrome or any syndrome known to be associated with developmental delay. As previously reported [66,67], mothers were native English speakers and had no past or present indication of major psychiatric illness as determined by medical chart review at time of enrollment. Maternal use of cocaine, as well as amphetamines, opiates, barbiturates, and benzodiazepines, was ascertained by interview, chart review at time of infant's birth, and by maternal and infant urine drug screens. While use of cigarettes, alcohol, and marijuana during pregnancy was also documented by interview and chart review, specific information on frequency and amount of use of these substances was not. Mothers estimated days of use of cocaine was also ascertained; only babies whose mothers reported cocaine use in at least two trimesters of pregnancy were included. Mothers who reported use of drugs other than tobacco, alcohol, marijuana, and cocaine were excluded from enrollment [66,67]. Since enrollment, the children have been evaluated semi-annually for measurements of growth, development, language, cognitive, and social-emotional outcomes [66,69,70,72,73]. Participant birth and childhood characteristics are shown in Table 1. The original cohort consisted of 224 participants (105 GCE participants and 119 Controls) enrolled at birth. During the ensuing years, five subjects died (1 GCE participant and 4 Controls), with an additional attrition of approximately 42% of GCE participants and 40% of Controls over the course of 12 years. Since this early attrition (largely related to inadequate number of study personnel secondary to fiscal constraints), cohort number has been stable for the past 8 years or more, with 120 participants (55% retention over 20 years) comprising the sample for the current report of NC function. GCE children lost to follow-up did not differ on any birth or maternal characteristics from those GCE children retained, including level of prenatal care ($p=0.74$), maternal drug screen positive for cocaine ($p=0.96$), birth weight ($p=0.45$), head circumference ($p=0.82$), exposure to alcohol, cigarettes or marijuana, admission to NICU, and discharge to biological mother ($p>0.20$). Further, those GCE children lost to follow-up did not differ from those retained in number of days of maternal cocaine use during pregnancy (95 vs. 99, respectively). Participants retained had longer length of neonatal stay in the hospital than those lost to follow-up, 8.7 versus 5.6, respectively ($p=0.031$). In the Control group, more males (60%) were lost to follow up than females (40%) ($p=0.042$). We expanded our examination of attrition by comparing scores on early cognitive outcomes for those lost to follow-up after age 12 months and those included in this report. One hundred and eighty two infants completed the 12 month assessment. Within this subset of participants, scores on the Bayley Scales of Infant Development for those lost to follow-up were similar to those retained at age 12 years ($p=.99$), with no interaction between cocaine exposure group and follow-up status.

Informed consent was obtained from participant caregivers and assent was obtained from all participants. The project was approved by the Institutional Review Board of the Children's Hospital of Philadelphia.

2.2. NC Assessments

Participants were assessed using a set of pencil and paper and computerized tasks designed to tax frontally and nonfrontally mediated NC systems defined by anatomical and functional criteria. While we understand that the whole brain is working during performance of each task, our strategy was to select tasks that disproportionately tax particular systems as

evidenced in the cognitive neuroscience literature cited below. Brief descriptions of NC systems assessed and tasks are listed below, with details available in other published reports [48,49]. The current report evaluates performance on a subset of 4 of the 7 systems presented previously [48,49]. The other three systems were either discontinued after assessment 2 or included tasks that were at ceiling in assessment 1 or 2, necessitating alternate tasks in subsequent assessments. The current report includes only tasks repeated across all three assessments. Systems evaluated include two frontal: Inhibitory Control, also referred to as Cognitive Control, and Working Memory, and two nonfrontal: Receptive Language and Incidental Memory. By examining performance of participants on a varied set of NC tasks we hope to better identify specific differences between GCE participants and Controls.

Executive Systems (Frontal)—*The Inhibitory Control system* was targeted to assess cognitive control processes and is closely linked to the anterior cingulate cortex in imaging and lesion studies. This system plays a crucial role in monitoring for conflict between the individual's automatic response and the correct response [25,30,95,106,113]. In addition, this system has been linked to the ability to summon additional attention needed to regulate responses. Task: Number Stroop [34,38] This computerized adaptation of the Counting Stroop requires participants to sort cards according to one of two sorting conditions. In the congruent condition, participants are timed as they sort the cards, as quickly as possible, according to the number (digit) shown on the card (e.g., the card with three "4 s" goes into the 4 pile). In the incongruent (conflict) condition, participants are timed as they do the same on the basis of the number of digits (e.g., three "4 s" goes into the 3 pile). The Stroop Effect is the reaction time difference in msec between the congruent and incongruent conditions. This task has the advantage over the classical Stroop Color and Word test in that it does not depend on skilled automatic reading (since poor readers will do paradoxically better on the classic Stroop). Functional neuroimaging studies have shown that for both Color and Counting Stroop the incongruent condition activates the ACC relative to the congruent condition [34].

Working Memory system, closely linked to the dorsolateral prefrontal cortex in imaging and lesion studies, allows an individual to hold the present context, rules, or goals in mind as a complex task is performed. Task: Spatial Working Memory [35]. This self-directed computerized task requires the subject search for hidden tokens one at a time within sets of four to eight randomly positioned boxes. Tokens are hidden only once in each box. Working memory skills are tapped as the subject, while searching, must hold in working memory the locations already checked and, as tokens are found, must remember and update the information about the locations of the found tokens [45]. In functional imaging studies, this specific task reliably activates dorsolateral prefrontal cortex [103–105].

Nonfrontal Systems—*The Language system* is shown in imaging and lesion studies to be localized to the left perisylvian region of the brain. Task: Peabody Picture Vocabulary Test (PPVT) [44]. The neuropsychological disorders which produce impairments in this task involve damage to left perisylvian system. The PPVT is a standardized receptive vocabulary test for children and adults between the ages of 2.5 through 90. On each trial, the subject hears a word and must select the corresponding picture from among four choices. This tests the lexical-semantic aspect of language. [58,94] Similar word-picture matching tasks used in functional neuroimaging studies also implicate the left perisylvian region [125,126].

The Memory system, shown in imaging research to map onto the medial temporal cortical area [89,124], is required for incidental or one-trial learning. Most standard memory tests are sensitive to both medial temporal and prefrontal function because performance is influenced by the subject's ability to organize the material to be learned and apply

mnemonic strategies [127]. In order to obtain a relatively pure measure of learning ability, we used incidental learning tests, in which the subject does not know that a memory test is to be administered when the to-be-remembered stimuli are presented [87]. Tasks: Incidental Word Memory. Patients with medial temporal damage do poorly on incidental word learning. In this picture word memory task, the subject views pairs of pictures [119,120], presented one pair per page, and is instructed to point to the member of the pair that cost less than \$20. Sometime later, during the test phase, the subject listens to a list of 80 words and decides which items were viewed earlier. For this task the total number of correct responses is recorded (total correct rejections + total correct hits) [89]. Incidental Face Memory. Medial temporal damage also impairs incidental learning of visual materials, including faces [88,89]. This task is analogous to the task with words, except that the learning set stimuli are photographs of faces, and the exposure to the initial set occurs as the participants judge whether the faces are likely to be a movie star or school teacher. During the test phase the child is presented with a series of 50 photographs and decides which faces were viewed earlier. For this task the total number of correct responses is recorded (total correct rejections + total correct hits). [23]

All tasks were carefully administered according to methods identified in the manuals and cognitive neuroscience literature to minimize errors due to methodological variance. All instructions were presented on the computer screen and the examiner read these aloud to the subject to ensure standardized administration across subjects. To eliminate administration and data processing errors we used computerized tasks for all but the standardized language measure. These careful data processing procedures were followed to ensure that results were truly representative of participant NC performance.

2.3. Other Measures

Other Exposures—At time of enrollment, mothers were asked about use of alcohol, cigarettes, and marijuana during pregnancy. Information was recorded as only “yes” or “no” without detailed tabulation of amount and frequency of use.

Measure of Childhood Intelligence—Children's Full Scale Intelligence Quotient (FSIQ) was assessed at age 6 years (6.1 ± 0.1) using the Wechsler Preschool and Primary Scale of Intelligence Revised Edition (WPPSI-R) [130].

Measure of Childhood Experience—Children's home environments were evaluated at age 4 (4.1 ± 0.2) and 8 years (8.4 ± 0.5) using the HOME Inventory. [27] The HOME is a structured 1-hour, in-home, parental interview and observational checklist with 8 subscales measuring specific aspects of the child's home life. In-home assessments were completed by a trained member of the research team masked to child exposure status. Previous studies have shown that environmental characteristics of parental nurturance and environmental stimulation are related to cognitive outcomes [32,48,51,60]. To examine the influence of these different aspects of the home environment we grouped HOME items to form two composite scores, Environmental Stimulation and Parental Nurturance [32,43,48,77]. The Environmental Stimulation composite incorporated HOME subscales most analogous to experiential factors that vary with environmental enrichment in animal studies. The Parental Nurturance composite incorporates HOME subscales that measured the warmth and availability of parental care. Composite scores were calculated by averaging the Z scores of relevant subscales for each age. Further details are described in Farah et al (2008) [48] which also shows these composites to be related to both general and specific aspects of cognitive function. In the current report, Environmental Stimulation and Parental Nurturance composites were computed by averaging the mean composites from the 4 and 8 year evaluations.

Foster Care Placement—At each study visit between birth and time of NC testing, the child's primary caregiver was recorded. We found 4 types of primary caregivers in our cohort: biological mother, biological father, kinship foster care, and non-kinship foster care. This information was then collapsed into the two categories, ever in foster care or never in foster care, used in analyses.

Measure of Maternal Depression—Children's primary caregivers were administered the Beck Depression Inventory-Second Edition (BDI-II) [16] at a study visit when the children were 11 years old. The BDI-II is an instrument designed to assess depressive symptoms in adults.

2.4. Testing Procedure

The NC assessments and all other evaluations included in this report were administered individually by a licensed clinical psychologist unaware of child exposure status. Each NC evaluation was completed in one visit to the research center and lasted an average of 2.5 hours, with 1 or 2 short break periods scheduled within the task administration. For the Stroop Task the difference between the congruent (text) and incongruent (number) conditions was computed and reversed to represent the Stroop Effect with higher scores indicating a better performance. For the Spatial Working Memory task we used the between search errors score which also was reversed so that higher scores indicated better performance. The aged referenced standard score for the PPVT was used in analysis of receptive language and the Total Correct scores for recall condition were used in the analysis of the two Incidental Memory tasks. All data for computerized tasks was processed using computer syntax files designed to transfer data from the testing software directly into the SPSS databases for statistical analysis. Preliminary analyses were performed to identify data irregularities, invalid subject response patterns, and outliers.

2.5 Power Analysis

We assumed that the intraclass correlation coefficient between the repeated measures of the outcome was 0.5. The effective sample size (based on independent observations) for this study with $N=120$ and three repeated measures is 180 [64]. Therefore, this study had statistical precision equivalent to a study in which 180 participants completed the study and in which no repeated measure is performed. A sample size of 180 participants will be sufficient to detect an effect size of 0.4 standard deviations with 80% power and type I error rate of 0.05. For example, using an estimated standard deviation for Stroop Effect score of 16.7 msec, the study is able to detect a Stroop score difference of 6.7 msec between the GCE and the control groups. Similarly, the differences that can be detected for Spatial Working Memory, PPVT, Incidental Word Memory, and Incidental Face Memory are 7.2 errors, 6.1 standard score points, 3.3 total correct responses and 1.7 total correct responses, respectively.

2.6 Statistical Analyses

To reduce the effect of outliers, data from each NC task were winsorized, that is, the two most extreme values at each end of the distribution of all children's scores were replaced with the third most extreme value at each end. We examined the effect of GCE on the outcomes and their change over time using the method of generalized estimating equations (GEE) [133,134]. Model I was an unadjusted model which included only cocaine exposure status, assessment number and their interaction. The three assessments were coded as -1, 0 and 1 respectively so that the coefficient of cocaine exposure status can be interpreted as its effort on the average of the outcome. In Model II, we then adjusted for potential confounding variables that are measured at baseline only including age at the first

assessment and gender. Finally, in Model III, we included the variables that are measured after GCE including environmental stimulation, parental nurturance and caregiver depression. Because of the concerns that the effect of GCE on outcomes may be attenuated by adjusting for the intermediate variables between GCE and outcomes, variables (e.g., birth weight, gestational age) that are potentially on the biological pathways between GCE and outcome were not included in the multivariable adjustment [14]. All analyses were done in SPSS. A p-value less than 0.05 was considered statistically significant.

3.0 Results

The figure shows box plots of task scores for each assessment for both GCE participants and Controls. These plots show increased scores for both groups across assessments for all tasks except the Incidental Face Memory. Of note, each of the PPVT median standard scores shown in the figure was below the average of the test standardization group of 100. We examined the relationship between tasks scores and 6-year FSIQ. All task scores from assessments 1 through 3 were related to 6-year FSIQ ($p < 0.02$), except for Incidental Word Memory at assessment 1 ($p=0.15$), Incidental Face Memory at assessment 2 ($p=0.062$) and Number Stroop at assessment 3 ($p=0.73$). (Data not shown.)

Table 2 shows the results of Models I and II for each of the five NC tasks. Model I, containing only GCE, Assessment Number and an interaction term, found no effect of either GCE or GCE x Assessment ($p \leq 0.11$). Except for Incidental Face Memory ($p=0.054$) all tasks showed increases over assessments ($p < 0.001$). Similar results are seen for Model II, which included Gender and Age at First Assessment.

Table 3 shows the final GEE model for each task. On the two frontal tasks, Stroop and Spatial Working Memory, we find no GCE effect and no association with any other covariates except Assessment Number (both $p < 0.001$) indicating that there is significant improvement in performance over ages 12–17 years. This association with age is consistent with the current developmental reports of continued prefrontal development through adolescence. [36,121,122]

Standard scores for the PPVT showed no relation to GCE, Age at First Assessment, Parental Nurturance and Maternal Depression (all $p \leq 0.26$). Males performed slightly better than females ($p < 0.058$) and performance on the task improved over time (Assessment Number: $p < 0.001$). As reported in previous analyses [48,65], PPVT scores were related to the Environmental Stimulation composite from the HOME Inventory ($p=0.039$). (See Table 3)

For the Incidental Word Memory task no overall GCE effect was observed, however, there was a statistically significant effect of GCE by Assessment Number ($p=0.031$), showing that scores for the GCE group increased at a slower rate than for Controls. The Incidental Faces Memory task showed GCE effects of borderline statistical significance ($p=0.055$) and scores on this task increased significantly with Assessment Number ($p=0.025$). No other covariates were related to this outcome including HOME composites, which had been shown previously to be associated with incidental memory performance [65]. (See Table 3)

Table 4 summarizes the GCE effects from Models I, II, and III. In repeated measures analyses such as GEE, group differences are tested in two ways, the difference between overall group means, represented by model coefficients for group alone, and the difference between change over time, represented by the coefficients for the interaction between group and assessment number. In the table these are shown as mean difference and slope difference, respectively.

4.0 Discussion

In this report we found no difference between GCE and Control adolescents on specific NC outcomes: inhibitory control, working memory, or receptive language. GCE effects of borderline statistical significance were observed on the Incidental Face Memory task, and a statistically significant GCE by Assessment Number interaction effect was seen on the Incidental Word Memory task. Determination of the exact mechanism causing this effect is challenging as many variables are included in the multivariable model. The reason that the association between GCE and memory is stronger in Model III than in Models I and II, may not just be due to the addition of in the environmental variables since the coefficients of other variables change as well. Nevertheless, by adding the environmental variables to the model, the relationship between GCE and the outcome changes which indicates that these additional variables act a confounder. Further investigation of these relationships is needed to clarify this interesting finding.

Participant performance on inhibitory control, working memory, and receptive language tasks improved over time. The longitudinal study design used in the current report consisted of multiple evaluations of the same NC constructs at ages 12, 14.5 and 17 years to allow for careful tracking of the behavioral correlates of developing brain systems thought to be affected by GCE [83,90]. This targeted study design revealed little evidence of latent effects of GCE in this sample of low SES adolescents. This finding is comparable to previous reports of similar levels of cognitive functioning in GCE participants and Controls from this low SES inner-city cohort [65,66,69–71].

We found that receptive language scores on the PPVT and both PFC system tasks, Stroop and Spatial Working Memory, increased with age. Scores on the incidental memory tasks did not show as robust a relation to age. These relations between age and NC performance are consistent with cross-sectional and longitudinal imaging studies of late childhood and adolescence showing that non frontal brain regions mature first, followed by frontal regions associated with working memory and inhibitory control [36,121,122].

Effects of Age, Gender and Environmental Stimulation were seen on the PPVT standard score. Scores increased an average of about 2 points across assessments at ages 12, 14.5 and 17 years. This change in age-adjusted standard scores reflects a small increase in language skills between early and late adolescence in this disadvantaged cohort. This small but statistically significant increase may be due to the participants increased access to technology and information during high school years. Males in this cohort performed better (+ 4.93 points higher) than females on average across the three assessments. Studies examining gender differences in verbal abilities have shown better performance in males [74], even though females are commonly thought to have better verbal skills [33,129]. A larger effect (5.91 standard score points) was seen for HOME Environmental Stimulation composite score. Equal to about a half a standard deviation difference, this is a clinically meaningful effect adds to the evidence that early cognitively stimulating experiences in the home environment are critical for later learning [28,29,32,59,60].

We included the HOME composites in our analyses because we previously found that language showed a strong relationship to HOME Environmental Stimulation composite and Incidental Memory scores showed a strong relation to the HOME Parental Nurturance composite [48]. In the current report as noted above, we find a strong relationship between language and environmental stimulation similar to that found in Farah et al (2008) [48]. We did not, however, find a relationship between incidental memory tasks and parental nurturance. We considered why we did not find this effect in this longitudinal analysis. First, the current report examines performance across 3 time points up to age 17 years, unlike the

previous report which examined performance at 1 time point only at age 12 years. Second, as children get older it is possible that the relation between childhood experience and later cognitive functioning is mitigated more by intervening variables associated with adolescence such as puberty and changes in social-emotional functioning and experience.

Of note, in Rao et al (2009) [108], we reported that hippocampal volume in adolescence was associated with parental nurturance experienced at age 4. This finding is consistent with animal studies reporting comparable relationships between early experience of maternal care and hippocampal measures. In the current report we chose to use the mean of the age 4 and 8 year Parental Nurturance score as used by Farah et al (2008) [48]. It may be that if we examined the relation between age 4 parental nurturance and incidental memory outcomes, we would have found a difference in the hippocampal memory function assessed in this report. In addition, the development of the hippocampus proceeds in an inverted u-shaped course with increasing volume early in adolescence until age 15 after which subsequent age-related changes are associated with decreased volume in these areas [57]. This developmental course is an example of the complex restructuring that occurs across adolescence. More in-depth analyses of these relations are needed to sort out the interesting patterns found in our cohort to date.

Despite the relatively robust findings in animal studies that GCE has a significant effect on cognitive outcomes, data from our cohort show no effects on three of five tasks assessed at three ages. GCE was substantial with median days of exposure equal to 99 days. Two methodological differences are apparent across the animal and human studies. First, variability in outcome associated with GCE in humans is undoubtedly attributable to the more complex context in which children develop, compared to experimental conditions in animal studies. Despite efforts to be comprehensive in their analyses of all factors associated with outcomes, researchers are unable to control for every risk factor that correlates with maternal cocaine use [18,19,40,41,86,90,91,96], whereas in animal studies these correlates are not present. Second, discrepancies between animal and human studies of GCE are likely related to the differences in how constructs are operationalized. Measures that are selected to evaluate outcome in children and to the timing of these assessments may be limited in comparability to those used in animal studies [6,37].

In our study we did control for a number of factors thought to be associated with outcomes including those listed in Table 1. The baseline model showed no cocaine effects, making covariate meditational analyses unjustified. Even when important covariates were added to the model we were not able to detect statistically significant effects. Tasks used in our study tapped components of important NC domains and have been used in other studies to examine NC function [46,49,50,65,100]. As noted above, each NC system was indexed using one task that was repeated across three ages (12, 14.5 and 17 years). These tasks typically take about 5 to 10 minutes to complete, and are embedded within a larger battery of tasks. The use of computerized tasks (Number Stroop, Spatial Working Memory, and Incidental Memory tasks) allows for more precise stimulus presentation and more accurate recording of subject responses. This methodology reduces the variance in scores that might be attributed to subtle differences in test administration or recording of subject responses by the examiner. Use of the PPVT allowed for standardized assessment of receptive language. This approach allowed for comparison of performance on the same exact task across three ages. While the tasks used were 1) based firmly in the cognitive neuroscience literature, 2) showed expected relations with age, and 3) were related to 6 year IQ scores, they tapped a restricted range of functioning within each NC system. For example, while receptive language is assessed, expressive language was not. With an expanded set of tasks, a more thorough examination of functioning for each NC system would be possible. In a previous

report that included a more comprehensive set of tasks but at only one time point, no GCE effects were observed [65].

More extensive evaluation of these NC domains must be completed as these tasks only tap a single component of these very complex NC constructs. Expansion of our longitudinal analysis is needed to include all tasks administered to participants despite changes in NC tasks across assessments. For example, Bandstra et al (2002) [10] in a longitudinal study of the effects of GCE on language functioning used two different language tests but using language performance z-scores at each age, was able to track changes in the language system between ages 3, 5 and 7 years. Applying a similar methodology to the performance data from our cohort may provide a more reliable and comprehensive index of these complex NC systems over time and expansion of our analysis of the GCE effects on the four systems. Understanding of the effects of GCE on performance on an expanded set of tasks and with repeated assessments may have yielded different findings.

There is accumulating evidence for the existence of subtle effects of GCE and their impact on the individual and society may be significant [80]. Small differences in cognitive outcomes may be linked to high risk problem behaviors and poor academic outcomes [81]. Some of the studies that report differences in language and attention have larger sample size and therefore are able to detect small but statistically significant cocaine effects. With a larger number of participants it is likely that the statistical significance level may have increased for some of our comparisons, highlighting the areas of functioning that are negatively affected by gestational cocaine exposure. The existence of small clusters of subtle effects may place children at increased risk for poorer outcome [82,98]. In this regard, we recently examined participant functioning using the following broad functional outcomes: teenage pregnancy, school failure, drug use, and adjudication [61]. We found no GCE effect on rates of these outcomes in our cohort. Instead, these outcomes were related to more proximal factors such as exposure to violence and characteristics of the home environment. Continued monitoring of long-term outcome is needed to determine if GCE leads to compromised child outcomes through adolescence and into adulthood.

While we were able to longitudinally evaluate NC functioning through adolescence this report has several limitations. First, sample size impacts our statistical power. It may be with a larger sample size we would have been able to detect effects GCE smaller than 0.04 standard deviation units for each outcome. Also, if statistically significant effects were detected in our cohort, tests of mediation would have been possible. In mediation models, first the relation between the independent and dependent variable must be statistically significant and this was not the case for our cohort [14]. Furthermore, as listed in Table 1, gestational exposures to cigarettes, alcohol, and marijuana were collinear with GCE. For example, 53 of the 55 GCE children were also exposed to prenatal tobacco leaving only 2 subjects in the GCE group who were not exposed to cigarettes. With this limited amount of variance in prenatal exposure to tobacco in the GCE group, controlling for this variable is not possible. Similarly, variance in foster care placement and participant race was limited. With more participants we may have been able to separate effects of these other important variables. Second, our subjects were all low SES which limits the generalizability of our findings to this demographic group. Using data from early evaluations of the home environment as well as caregiver variables assessed across childhood, we show that these factors are more salient to cognitive development than prenatal exposures. These results also add to the existing literature showing the importance of early childhood environmental factors on developmental outcomes [26,28,29,32,59]. With more variability in SES we may have been able to identify effects of GCE in children who have access to more enriched environments associated with families that have access to more financial and emotional resources [60].

It may be possible that some women who used cocaine were misclassified as controls at study entry. Our study was designed to minimize this possibility, as we required negative history and negative urine screens on both mother and baby for inclusion. Further, maternal profiles of the two groups were quite different. Nevertheless, we cannot entirely exclude the possibility that some women were misclassified. We also considered that we might have enrolled women who were not heavy cocaine users. We doubt this as 88% of our cocaine-using mothers had urines positive for cocaine metabolites at delivery (data not shown) [67], a marker suggested by Zuckerman et al [136] to identify frequent users. Further, we enrolled only women who used in two or more trimesters of pregnancy, with 99% of our mother using in all three trimesters; the top quartile of self-reported days of use in pregnancy in our cohort was 195 days or more.

We examined the possibility results are affected by attrition in our cohort. It is not likely that we would have found a difference in those we retained because levels of GCE were similar to those lost to follow up. While there were more males lost to follow up and because some gender effects are reported by others [102], it may be that with lower rates of attrition of males, we could have observed an interaction between cocaine exposure and gender. As noted above, we had sufficient power to detect differences with effect sizes of at least 0.40. In this regard, with a lower overall attrition rate, our study would have had increased power to detect smaller differences between groups which in turn would allow for determination of the clinical significance of the smaller GCE effects over time.

In summary, this carefully conducted study spanning adolescence shows no effects of GCE on inhibitory control, working memory or receptive language. While cocaine exposure was not related to Incidental Memory in baseline models, addition of environmental covariates to these models revealed that on the Incidental Word Memory task scores for the GCE group increased at a slower rate than for controls and on the Incidental Face Memory task control participants scored higher than GCE participants. Our results provide additional evidence that environmental variables such as those assessed in the HOME Inventory influence cognitive outcomes. As shown here and elsewhere the cognitive performance of our cohort is below average, suggesting that overall effects of poverty are placing GCE and Control children at a clinically significant disadvantage compared to other children their age. An important priority for those who care for GCE children and all children born into high risk environments is to address the problems that contribute to their disadvantage, including not only maternal drug use but also limited access to resources needed to provide cognitively and emotionally stimulating experiences early in life.

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Abbreviations

BDI-II Beck Depression Inventory - II

FSIQ	Full Scale Intelligence Quotient
GCE	Gestational Cocaine Exposure
GEE	Generalized Estimating Equations
HOME	Home Observation for Measurement of the Environment
NC	Neurocognitive
PPVT	Peabody Picture Vocabulary Test
PFC	Prefrontal Cortex
SES	Socioeconomic Status
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence – Revised Edition

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Figure 1.

Box plots of neurocognitive task scores for Control and GCE groups at Assessments 1, 2 and 3. Controls are open plots, GCE are shaded plots. The box represents the 25th and 75th percentiles of the distributions with the median marked in the middle. Whiskers are the 10th and 90th percentiles. Outliers are dots above and below the box plot.

Table 1

Participant Characteristics by GCE Status

	GCE (n = 55)	Control (n = 65)	p-value
At Time of Birth			
Gender, Female (n (%)) ^a	31 (56%)	37 (57%)	1.00
Gestational Age (GA), weeks (Mean ± SD)	37.5 ± 2.1	39.1 ± 2.0	<0.0005
Birth Weight, kg (Mean ± SD)	2.6 ± 0.5	3.1 ± 0.6	<0.0005
Birth Weight <10 th % ile for GA	4 (7%)	2 (3%)	0.41
Head Circumference, cm (Mean ± SD)	32.1 ± 1.7	33.5 ± 1.6	<0.0005
Head Circumference <10 th % ile for GA	9/54 ^b (17%)	3 (5%)	0.036
Race, African American	52 (94%)	64 (98%)	0.33
Other Gestational Exposures			
Alcohol (n (%))	30 (54%)	5 (8%)	<0.0005
Marijuana (n (%))	25 (45%)	2 (3%)	<0.0005
Tobacco (n (%))	53 (96%)	14 (21%)	<0.0005
Gestational Cocaine Exposure, days (Median)	99 (7, 273)	0 (0, 0)	<0.0005
Maternal Age, years (Mean ± SD)	27.2 ± 4.3	22.4 ± 5.4	<0.0005
During Childhood			
Age at Assessment 1, years (Mean ± SD) ^a	12.3 ± 1.3	11.9 ± 1.2	0.074
Age at Assessment 2, years (Mean ± SD)	14.7 ± 0.9	14.5 ± 0.8	0.19
Age at Assessment 3, years (Mean ± SD)	17.5 ± 0.9	17.0 ± 0.9	0.01
Wechsler Full Scale IQ at age 6 (Mean ± SD)	82.3 ± 13.6	82.6 ± 12.3	0.91
Any Foster Care Placement (n (%))	26 (47%)	8 (12%)	<0.0005
HOME Score at age 4	40.4 ± 7.6	44.2 ± 5.5	0.003
HOME Score at age 8	47.6 ± 5.0	49.5 ± 3.4	0.028
HOME Composite Scores			
Parental Nurture (mean of age 4 and 8) ^a	-0.09 ± 0.77	0.11 ± 0.46	0.11
Environmental Stimulation (mean of age 4 and 8) ^a	-0.17 ± 0.78	0.16 ± 0.52	0.008
Caregiver BDI-II Depression Score ^a	10.0 ± 8.9	8.8 ± 9.3	0.46
Caregiver Current Cocaine Use (n (%))	30 (54%)	5 (8%)	<0.0005

^a Candidate Covariates used in GEE models;

^b Missing data from one subject.

Table 2
Model I and Model II for Analyses of GCE Effects on Outcomes Using Generalized Estimating Equations

Predictor	Number Stroop	Spatial Working Memory	PPVT	Incidental Word Memory	Incidental Face Memory
Model I					
Intercept	-16.82 (1.12) ^a	-36.28 (1.64)	90.28 (1.81)	62.49 (0.57)	45.12 (0.29)
GCE	-0.19 (1.72)	-3.13 (2.52)	-2.11 (2.56)	-0.69 (1.05)	-0.80 (0.49)
Assessment No.	10.81 (1.25)	10.06 (1.23)	2.37 (0.74)	4.09 (0.80)	0.18 (0.30)
GCE x Assessment No.	1.52 (1.75)	0.18 (1.78)	1.74 (1.09)	-1.76 (1.12)	0.70 (0.55)
Model II					
Intercept	-33.25 (7.76)	-60.18 (11.26)	101.89 (11.99)	63.72 (4.18)	41.82 (2.30)
GCE	-0.64 (1.71)	-3.83 (2.48)	-1.79 (2.54)	-0.63 (1.04)	-0.89 (0.49)
Assessment No.	10.80 (1.26)	10.08 (1.22)	2.37 (0.75)	4.08 (0.80)	0.18 (0.30)
GCE x Assessment No.	1.50 (1.75)	0.32 (1.77)	1.74 (1.09)	-1.77 (1.12)	0.71 (0.55)
Age at first Assessment	1.22 (0.65)	2.11 (0.92)	-0.84 (1.00)	-0.15 (0.34)	0.28 (0.19)
Gender (Female)	3.52 (1.70)	-2.01 (2.33)	-2.88 (2.58)	0.88 (1.02)	-0.12 (0.49)

^a Coefficient (SE);

^b p-value

Table 3
Model III for Analyses of GCE Effects on Outcomes Using Generalized Estimating Equations

Predictor	Number Stroop		Spatial Working Memory		PPVT		Incidental Word Memory		Incidental Face Memory	
Intercept	-35.38 (10.07) ^a	0.001 ^b	-61.63 (14.42)	<0.001	97.70 (14.32)	<0.001	60.26 (5.82)	<0.001	40.88 (2.88)	<0.001
GCE	1.67 (1.85)	0.37	-3.60 (2.66)	0.18	-2.89 (2.58)	0.26	-0.24 (1.14)	0.83	-1.02 (0.53)	0.055
Assessment No.	11.14 (1.43)	<0.001	10.16 (1.41)	<0.001	2.72 (0.80)	<0.001	4.20 (0.94)	<0.001	0.42 (0.30)	0.025
GCE x Assessment No.	1.71 (1.98)	0.39	0.32 (2.01)	0.87	0.58 (1.16)	0.51	-2.69 (1.24)	0.031	0.55 (0.61)	0.37
Age at 1 st Assessment	1.37 (0.83)	0.098	2.02 (1.16)	0.081	-0.36 (1.17)	0.76	0.14 (0.47)	0.77	0.35 (0.24)	0.14
Gender (Female)	3.11 (1.79)	0.083	-2.41 (2.48)	0.33	-4.93 (2.60)	0.058	0.89 (1.10)	0.42	-0.42 (0.50)	0.40
Parental Nurture	2.10 (1.91)	0.27	1.72 (2.71)	0.53	-0.31 (2.25)	0.89	0.49 (1.12)	0.66	0.77 (0.50)	0.12
Environmental Stimulation	-0.05 (1.70)	0.98	0.65 (2.31)	0.78	5.91 (2.86)	0.039	1.24 (1.08)	0.25	0.84 (0.54)	0.12
Caregiver BDI-II Depression Score	0.07 (0.10)	0.50	0.14 (0.14)	0.33	0.03 (0.13)	0.84	-0.04 (0.07)	0.62	0.03 (0.02)	0.16

^a Coefficient (SE);

^b p-value

Table 4

Summary of GCE Effects from Models I, II, and III

Outcome	GCE vs. Control	Model I		Model II		Model III	
		Coeff	p-value	Coeff	p-value	Coeff	p-value
Number Stroop	Mean difference	-0.19	0.91	-0.64	0.71	1.67	0.37
	Slope difference	1.52	0.39	1.50	0.39	1.71	0.39
Spatial Working Memory	Mean difference	-3.13	0.21	-3.83	0.12	-3.60	0.18
	Slope difference	0.18	0.92	0.32	0.86	0.32	0.87
PPVT	Mean difference	-2.11	0.41	-1.79	0.48	-2.89	0.26
	Slope difference	1.74	0.11	1.74	0.11	0.58	0.51
Incidental Word Memory	Mean difference	-0.69	0.51	-0.63	0.55	-0.24	0.83
	Slope difference	-1.76	0.12	-1.77	0.12	-2.69	0.031
Incidental Face Memory	Mean difference	-0.80	0.11	-0.89	0.070	-1.02	0.055
	Slope difference	0.70	0.21	0.71	0.20	0.55	0.37

Model I: GCE, assessment No and GCE by assessment number interaction

Model II: model I plus age at first assessment and gender

Model III: model II plus parental nurturance, environmental stimulation and Caregiver depression

Table 5

NC task scores for Control and GCE groups at Assessments 1, 2 and 3

	GCE (n = 55)	Control (n = 65)
Number Stroop (Reaction Time Difference, reversed)		
Assessment 1	-29.7 ± 18.0 ^a	-28.3 ± 17.7
Assessment 2	-16.2 ± 11.9	-15.3 ± 11.8
Assessment 3	-5.1 ± 9.7	-6.8 ± 10.1
Spatial Working Memory (Between Search Errors, reversed)		
Assessment 1	-48.8 ± 15.4	-46.7 ± 17.3
Assessment 2	-41.5 ± 15.0	-35.5 ± 14.1
Assessment 3	-28.2 ± 19.6	-26.6 ± 16.8
PPVT (Standard Score)		
Assessment 1	83.7 ± 12.4	87.8 ± 13.8
Assessment 2	89.5 ± 16.9	90.7 ± 16.7
Assessment 3	91.5 ± 15.2	92.8 ± 15.1
Incidental Word Memory (Recognition Total Correct)		
Assessment 1	59.6 ± 7.6	59.1 ± 6.6
Assessment 2	61.4 ± 5.4	60.9 ± 5.8
Assessment 3	64.3 ± 11.3	67.4 ± 9.1
Incidental Face Memory (Recognition Total Correct)		
Assessment 1	42.2 ± 6.1	44.0 ± 3.5
Assessment 2	47.5 ± 2.2	47.4 ± 2.0
Assessment 3	43.8 ± 4.1	44.4 ± 3.7