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Children With and Without Gestational Cocaine Exposure: A Neurocognitive Systems Analysis

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1. INTRODUCTION

An extensive preclinical literature documents the deleterious effect of cocaine on prenatal brain development and subsequent function in animals. One mechanism by which cocaine affects brain development is by a reduction in uterine blood flow and subsequent fetal hypoxia [65, 87]. Cocaine also disrupts the neural ontogeny of the monoaminergic neurotransmitters, which include dopamine, norepinephrine, and serotonin [45,62]. This disruption may affect brain development globally as well as impact the structure and function of specific systems. In this regard, anatomical, physiological, and behavioral abnormalities have been found in animals with gestational cocaine exposure (GCE) [26,38–40,79]. The systems most reliably affected by GCE in animals include the executive/attentional systems of prefrontal cortex and memory [38–40].

In contrast, the empirical literature on humans is inconsistent, with some studies finding cognitive impairments and others finding no effect of GCE [8,11,35,49,50,56,57,66,73,77, 83]. One complicating factor is that children with GCE are more likely to have a number of other developmental risk factors, both medical and psychosocial, than children without such exposure. For example, cocaine using mothers are more likely to use other drugs, to have poorer nutrition, and to have less stable home lives [55,81]. Failure to control for these potential confounds would inflate estimates of the impact of GCE.

An earlier review of the effects of GCE on human brain and behavioral development in young children was published by Frank, et al [34]. After excluding studies that lacked control groups, failed to blind examiners to group membership, did not prospectively enroll participants, or suffered from other serious methodological limitations, the authors were left with 36 studies. On the basis of these studies, all of which were conducted with children aged six years or younger, the authors concluded that: “there is no convincing evidence that prenatal cocaine

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exposure is associated with developmental toxic effects that are different in severity, scope or kind from the sequelae of multiple other risk factors.” This review demonstrated that many findings once thought to be specific effects of gestational cocaine exposure are correlated with other factors, including prenatal exposure to tobacco, marijuana and/or alcohol and the quality of the child’s environment [25,34,80].

More recently published studies, controlling for a number of medical and social risk factors, report finding differences between exposed and non-exposed children on measures of language [5,57,67], attention [1,68,72,75] and perceptual reasoning [77]. For many of these studies, effect sizes are small [5,57,67], with findings often limited to single rather than multiple components of language and attention [68,75]. However, these effects may prove meaningful because underlying abnormalities in cognitive processing, such as language processing, attention, and perceptual reasoning, are associated with learning disorders and associated problems in school [2].

Some studies examining the relation between cocaine exposure status and school performance have found a higher incidence of learning disability in exposed subjects [56,66]. Morrow et al [66] report that cocaine exposed children were 2.8 times more likely to develop a learning disability by age 7. On the other hand, in the same cohort as for this report, Hurt et al [49] examined the grade retention patterns and reported no effect of cocaine exposure on grade retention patterns through grade 4 after controlling for important covariates. In this study, while GCE was associated with a higher rate of commission errors on a distractibility task, and higher distractibility was associated with higher rates of grade retention, no reliable relation between cocaine exposure and grade retention was established. Similarly, Singer et al, [77] in a recent, well controlled evaluation examining both IQ and school achievement, found cocaine effects on only the Perceptual Reasoning composite score of the Wechsler Intelligence Scale for Children – Fourth Edition and reported no effects on domains of academic achievement. Given these varied results, continued investigation of effects of gestational cocaine exposure on specific cognitive processes through school age are necessary for improved understanding of the long term outcomes of these at risk children.

Across various studies, cocaine effects have been identified in the cognitive domains of language [5,57,67], attention [1,68,72,75] and perceptual reasoning. The present study was designed to assess effects of GCE on these cognitive skills specifically, as well as on other important cognitive domains, while controlling for important covariates that are likely to impact development. Each domain that is assessed in this report is either prefrontally mediated and responsible for the control of attention, working memory, and decision making, or non-prefrontally mediated and responsible for processing language, declarative memory, spatial cognition, and visual cognition. The study also was motivated by the need to address GCE effects at older ages, given the possibility of so called “ sleeper” or latent effects [36,63,78]. The subjects for the investigation reported here were middle school-aged children with and without GCE. They were assessed with tasks adapted from the cognitive neuroscience literature to tap seven specific neurocognitive (NC) systems: Cognitive Control, Working Memory, Reward Processing, Language, Memory, Spatial Cognition, and Visual Cognition. Multivariate analysis of these NC systems allowed for examination of general multivariate effects on cognitive function as well as specific between-subject effects on individual NC systems.

2. METHODS

2.1. Subjects

Our subjects were 120, primarily African American, middle school-aged children, approximately half with gestational cocaine exposure and half without. 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 socioeconomic status (SES) as defined by maternal receipt of public medical assistance. Birth characteristics for GCE and Control subjects included in this report are shown in Table 1. None of the children had Fetal Alcohol Syndrome or any syndrome known to be associated with developmental delay. As previously reported [47,48], 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, medical record review at time of birth, and by maternal and infant urine specimens. Mothers who reported use of drugs other than tobacco, alcohol, marijuana, and cocaine were excluded from enrollment in the study [47,48]. Mothers' estimated days of use of cocaine use was also ascertained through maternal interview at time of enrollment in the study. Only mothers who reported cocaine use in at least two trimesters of pregnancy were included. While use of cigarettes, alcohol, and marijuana during pregnancy was also documented by interview and medical record review, specific information on frequency and amount of use of these substances was not.

Since enrollment, the children have been evaluated semi-annually for measurements of growth, development, language, cognitive, and social-emotional outcomes [47,50,51]. Two hundred twenty-four (105 GCE and 119 Controls) subjects were enrolled at birth. During the ensuing years, five subjects died (1 GCE and 4 Controls), with an additional early attrition of approximately 40% of Controls and 42% of GCE. 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 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 such variables as level of prenatal care, maternal drug screen positive for cocaine, birth weight, head circumference, exposure to alcohol, cigarettes or marijuana, admission to NICU, and discharge to biological mother ($p > 0.20$). Further, those lost to follow-up did not differ from those retained in number of days of maternal cocaine use during pregnancy ($p = 0.61$). The only statistically significant difference found between those lost to follow-up and those retained was in the Control group, with more males (60%) lost to follow up than females (40%) ($p = 0.042$).

Assent was obtained from all participating subjects and informed consent was obtained from their caregivers. The project was approved by the Institutional Review Boards of the University of Pennsylvania and the Children's Hospital of Philadelphia.

2.2. NC Assessment

NC functioning was evaluated at subject mean age of 12.1 years, using a battery of 'pencil and paper' and computerized tasks designed to tax three frontal and four non-frontally 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. We selected two representative tasks per NC system, with each task chosen to be as different as possible from the other in terms of stimulus and response types. Brief descriptions of NC systems assessed and tasks are listed below, with details available in other published reports [31,32].

Executive Systems (Frontal)—*The Cognitive Control system*, closely linked to the anterior cingulate cortex in imaging and lesions studies, plays a crucial role in monitoring for conflict between the individual's automatic responses and the correct response. In addition,

this system has been linked to the ability to summon additional attention needed to regulate responses. Tasks: Go-NoGo; Number Stroop [17,21].

The Working Memory system, closely linked to the dorsolateral prefrontal cortex in imaging and lesions studies, requires the ability to hold the present context, rules, or goals in mind as the individual performs a complex task. Tasks: Spatial Working Memory; Letter Two-Back [18,19].

The Reward Processing system, associated with the ventromedial prefrontal cortex in imaging and lesions studies, underlies an individual's ability to resist the pull of reward stimuli. Tasks: Delay task from the Gordon Diagnostic System; Intra/Extra Dimensional (ID/ED) Shift task [18,43].

Non-executive Systems (Non-frontal)—*The Language system*, shown in imaging and lesion studies to be linked to the left perisylvian cortical area, underlies two main and distinct components of language: lexical semantics and syntax. Tasks: Peabody Picture Vocabulary Test (PPVT); Test for the Reception of Grammar (TROG) [13,27].

The Memory system, shown in imaging research to map onto the medial temporal cortical area, is required for incidental or one trial learning. Tasks: Incidental Word Learning; Incidental Face Learning [60].

The Spatial Cognition system, shown in imaging and lesion studies to activate the parietal cortical area [14,70], subserves the representation and manipulation of spatial information. Tasks: Line Orientation; Mental Rotation [28].

The Visual Cognition system, linked in imaging and lesion studies to the occipito-temporal brain region, subserves the segmentation and recognition of shapes. Tasks: Shape Detection from Warrington and James' Visual Object & Space Perception (VOSP) Battery; Face Perception from Mooney's Test of Visual Closure [64,84].

2.3. Cocaine Exposure

Two measures of cocaine exposure were examined. In our main analyses we included a dichotomous, "yes" or "no" variable for cocaine exposure status based on maternal interviews and urine drug screens at birth. To examine the possibility of a dose effect, we computed an estimation of days of gestational cocaine exposure. During the enrollment interview, at the time of the child's birth, mothers were asked to indicate frequency of cocaine use by trimester on a 10 item scale that ranged from: "no use" to "2–3 times per week" to "three or more times per day". Days of use were estimated from these responses.

2.4. Other Measures

Other Exposures—At time of enrollment, mothers were asked about use of alcohol, cigarettes, and marijuana during pregnancy and use of these drugs during pregnancy was documented in yes / no format for each participant. These dichotomous indicators of other prenatal exposures were used in analysis.

Measure of Childhood Intelligence—Children's Full Scale Intelligence Quotient (FSIQ) was assessed at age 6 years using the Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R) [85].

Measure of Childhood Experience—Children's home environments were evaluated at age 4 years (4.1 ± 0.2) and 8 years (8.4 ± 0.5) using the Home Observation for Measurement of the Environment (HOME) Inventory [15]. The HOME is a 1-hour structured, 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. Studies in cognitive neuroscience have shown that environmental characteristics of parental nurturance and environment are related to neurocognitive outcomes [33]. We have found similar relationships in our cohort, with HOME composites related to both general and specific aspects of cognitive function [31]. We included these important variables in the current analysis. The Environmental Stimulation composite incorporated HOME subscales most analogous to experiential factors that vary with environmental enrichment in animal studies. The Parental Nurturance composite incorporated 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 [31]. The means of the four and eight year Environmental Stimulation composites and the four and eight year Parental Nurturance composites were used in this report.

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 caregiver in our cohort: biological mother, biological father, kinship foster care and non-kinship foster care. These were then collapsed into two categories: ever in foster care and never in foster care. These categories were used to compute the dichotomous yes/no variable used in analysis.

Measure of Maternal Depression—Children's primary caregivers were administered the Beck Depression Inventory-Second Edition [7], (BDI-II) during the visit one year prior to the child's NC evaluation. The BDI-II is an instrument designed to assess depressive symptoms in adults.

2.5. Testing Procedure

The NC task battery, as well as all evaluations included in this report, was administered individually by a licensed psychologist unaware of child exposure status. The neurocognitive evaluation was completed in one study visit lasting an average of 2.5 hours, with 1 or 2 short break periods scheduled within the task administration. Also, at each study visit, demographic information was updated to include information about the current primary caregiver and household environment.

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.

In order to express performance on a common scale for purposes of analysis, the data for each task were transformed to Z scores defined relative to the distribution of all 120 children. Composite scores for each NC system were then created by averaging the Z scores for the two tasks used to assess each system.

Effects of GCE on NC function were tested using multivariate analysis of covariance (MANCOVA). The seven NC system composite scores were entered as the multivariate dependent variable. Using Multiple Analysis of Variance (MANOVA), we examined the relation between the seven NC system composite scores and individual birth and school-age characteristics shown in Table 1 and Table 2. Table 3 shows the results of univariate testing of the relations between NC outcome and important covariates. Those covariates that were related to outcome at $p < 0.20$ were subsequently examined using MANCOVA. Of variables measured at birth, this included only prenatal exposure to alcohol. Of those measured during

school age years, it included age at testing, foster care placement, caregiver current cocaine use, and the Parental Nurture HOME composite.

We tested the relation of GCE to NC outcome using a series of MANCOVA models designed to maximize our degrees of freedom for analysis by eliminating nonsignificant covariates ($p > .10$) after each model analysis (Table 4 Models 1 to 5). Because age is robustly associated with cognitive development, this variable was included in all analyses. GCE status, our main independent variable of interest was also included in all models. While MANOVA showed no statistically significant effects of gender on outcome (see Table 3), we included this variable in model 2 to determine if there were differential effects of GCE on outcomes by gender [8, 11, 39], a finding previously reported by others. Also, because others have reported an association between cognitive outcomes and prenatal exposure to cigarettes and marijuana [22, 37, 46, 57], and environmental stimulation in the home [31, 44, 53], we included these variables in our analysis.

We first examined the effects of GCE alone, including no covariates in the model (Model 1), followed by a MANCOVA that included age at testing, gender, prenatal exposure to cigarettes, alcohol or marijuana, (Model 2). Next, we added the two composites of childhood experience from the HOME: Environmental Stimulation and Parental Nurture composites (Model 3), followed by caregiver related variables: foster care placement and caregiver current cocaine use (Model 4). Finally, a dose response effect was examined by analyzing GCE as a continuous rather than categorical variable in the GCE group (Model 5).

2.7. Power Analysis

Assuming a correlation coefficient of 0.4 among the seven NC outcomes and a sample size of 120, there was 80% power (type I error = 0.05) to detect a significant difference between the GCE and Control if there was at least one NC outcome with an effect size of 0.5 or greater. With a sample size of 120, inclusion of up to 6 additional variables is acceptable for MANCOVA analysis of the effects of GCE.

3. RESULTS

First, we present descriptive statistics for individual NC tasks. The means, standard deviations and ranges of scores for each group in each task are presented in Table 2 for the purpose of indicating that performance differences would not be obscured by ceiling or floor effects. By independent samples t-test there were no differences between groups (data not shown). As shown in Table 2, standard scores for the language measures were in the low average range while working memory and reward processing task scores were in the average range, with all scores falling below the mean for the standardization sample. This pattern of performance is consistent with previous reports on our cohort as well as other groups of disadvantaged children showing poorest performance in verbal tasks.

Subjects were close to the ceiling on one task of visual cognition, the VOSP, as indicated by mean scores of 19.1 out of 20. As this could impair our ability to discern the effects of GCE on performance, data from this task were excluded from the current analysis. Also, due to its late addition to the battery, the Gordon Delay task was available for only 80 subjects. Thus, data from this task were also excluded from the current analysis. For the Visual Cognition and Reward Processing systems, after exclusion of the VOSP and Gordon Delay tasks respectively, the Z score for the single remaining task was used in subsequent data analyses

3.1. Effects of GCE on NC function, with and without covariates

A MANOVA, simply testing the effects of GCE on the seven NC system composite scores, showed no overall effect of GCE on NC function, $F(7,108)=1.09$, $p=0.37$ (Table 4, Model 1). After adjustment for multiple comparisons, there were no significant univariate effects of GCE on individual NC systems (Data not shown).

When age at testing, gender and the exposures to cigarettes, alcohol and marijuana were added to the analysis (Table 4, Model 2), there was still no overall effect of GCE, $F(7,100)=0.96$, $p=0.47$. Age showed a strong effect, $F(7,100)=3.23$, $p=0.004$, and gender, $F(7,100)=0.88$, $p=0.53$, showed no effect on NC outcome. There was no interaction effect between GCE and gender, $F(7,100)=0.37$, $p=0.92$. Exposure to alcohol, $F(7,100)=2.16$, $p=0.045$, was significantly related to the multivariate outcome; however, prenatal exposure to cigarettes, $F(7,100)=2.027$, $p=0.059$, showed only a borderline association with the outcomes and prenatal exposure to marijuana, $F(7,100)=0.48$, $p=0.85$, showed no effect on outcome.

Next, we examined environmental covariates using HOME composites. One hundred and sixteen of the 120 subjects who completed the NC evaluation also had HOME scores available for these analyses. In the MANCOVA retaining GCE status, age at testing, prenatal cigarette and alcohol exposure (with gender and the exposure to marijuana removed), we added HOME Parental Nurturance and Environmental Stimulation composites (Table 4, Model 3). No effects of GCE were seen, $F(7,97)=.968$, $p=0.46$. The Environmental Stimulation composite, $F(7,97)=2.51$, $p=0.020$, as well as age at testing, $F(7,97)=4.36$, $p<0.001$, was associated with overall NC function. The Parental Nurturance composite was not related to overall NC function, $F(7,97)=0.95$, $p=0.47$, and prenatal alcohol exposure was no longer associated with outcome, $F(7,97)=1.56$, $p=0.16$, in this model.

Finally, we evaluated whether current caregiver variables, foster care placement and caregiver current cocaine use, would impact our outcome measure. Of the 120 children, 34 had a history of foster care placement (See Table 1), of these only 9 (6 GCE and 3 Controls) were ever in non-kinship care with 2 subjects (1 GCE and 1 Control) in non-kinship foster care for the majority of their lives. Because of low prevalence non-kinship care, we collapsed our foster care placement data to reflect two groups: ever in foster care and never in foster care. To investigate these relationships, we performed a MANCOVA retaining GCE status, age at testing, prenatal cigarette exposure, and the HOME Environmental Stimulation composite, excluding the Parental Nurturance composite, gender and prenatal alcohol exposure, and adding foster care placement and caregiver current cocaine use variables to the model (Table 4, Model 4). No overall effect of GCE, $F(7,99)=1.34$, $p=0.24$, foster care placement, $F(7,99)=1.51$, $p=0.17$, or caregiver current cocaine use, $F(7,99)=1.74$, $p=0.11$, was seen. Age at testing, $F(7,99)=3.66$, $p=0.001$, and the HOME Environmental Stimulation composite, $F(7,99)=2.58$, $p=0.017$, continued to show a strong effect on outcome. Prenatal cigarette exposure effects were nonsignificant, $F(7,99)=1.92$, $p=0.074$.

3.3. Further Analyses

To examine the possibility of a dose effect of cocaine exposure on the multivariate NC outcome, the number of days of GCE (median days of GCE = 99), and age at testing and HOME Environmental Stimulation composite were modeled using MANCOVA. Only GCE subjects were included in this analysis. The cigarette exposure variable, significant at $p<.10$ in each model analysis, was not included in this model because only 2 of the 55 GCE children had no prenatal cigarette exposure. MANCOVA, with days of cocaine exposure, showed no overall effect of days of GCE on NC function, $F(7,43)=0.98$, $p=0.46$, and in this group, age at testing, $F(7,43)=1.55$, $p=0.18$, and HOME Environmental Stimulation composite, $F(7,43)=0.80$, $p=0.59$, were not related to the outcome (Table 4, Model 5).

Because we did not find effects of GCE on NC outcome, we performed an analysis to determine if this NC battery, designed to tax specific frontal and non-frontal NC systems as shown by neuroimaging and lesion studies, served as a valid index of cognitive ability. We used two indicators of validity, the increase in NC test scores with age and the relation of NC scores to scores on other tests of cognitive functioning [3]. In a MANCOVA including age at testing and Wechsler Full Scale IQ score as covariates, the effects of both age at testing, $F(7,96)=6.01$, $p<0.001$, and IQ, $F(7,96)=19.23$, $p<0.001$, were seen. Six of the seven NC composites showed a relation to age (all $p<0.05$, except for the visual cognition composite, $p>0.3$) and all seven NC composite scores showed a relation to IQ (all $p<0.02$). These results add to the validation of our NC battery as we have shown a developmentally appropriate increase in cognitive functioning with age and a relation to other tests of cognitive ability [3].

4. DISCUSSION

For this cohort of middle school-aged children, we found no evidence of impaired NC function caused by gestational cocaine exposure, despite the fact that our sample size was adequate to detect a statistically and clinically significant difference (effect size of 0.5) and we used a NC battery shown to be sensitive to age and IQ. This is an unexpected result in view of the well-established preclinical effects of cocaine on uterine blood flow and fetal oxygenation [65,87] as well as its effects on developing monoaminergic neural systems [26,45,62]. While previous studies in humans have shown specific effects of GCE on language [5,57,67], attention [1, 68,72,75] and perceptual reasoning [77], we found no difference between groups even with isolation of specific cognitive systems for evaluation of cocaine effects. Controlling for multiple confounding child and environmental variables also did not reveal any effects of GCE. Since most of the GCE children in our cohort were heavily exposed [82,88] (median days of maternal cocaine use during pregnancy was 99), the lack of GCE effects in our sample is even more striking. Nonetheless, after addressing factors important for isolation of GCE effects on children, we found no difference between children with GCE and Controls.

While we reported early differences between GCE and Controls in birth weight, head circumference, gestational age, as well as maternal age, and later history of foster care placement, we still found no effects of GCE on NC outcome in this sample of low SES children. Our results may reflect, in part, the limited variation in our cohort of gestational age and foster care, two variables known to impact development. These special characteristics of our cohort limited exploration of certain questions. First, the children in this cohort were limited to those born at term or near term so that the serious effects associated with prematurity could be minimized. These children were not at increased risk of developmental problems secondary to prematurity as they were enrolled only if they were greater than or equal to 34 weeks gestational age at birth. Thus, we could not examine the compound risk of GCE and prematurity. We did, however, evaluate effects of gestational age as shown in Table 3 and found no effects in our cohort of children born at term or near term. Second, between birth and age at testing for this report, all but two of the children (1 GCE and 1 Control) who were placed in foster care were adopted by relatives or placed with familiar adults (grandparents, aunts, uncles).

While children placed in non-kinship foster or adoptive care have been shown to have better outcomes than GCE children in kinship placements [77], we were unable to examine such effects in our cohort because of small cell size for the non-kinship foster care category ($n=2$). Perhaps with a larger sample size we would have had enough variance in caregiver categories to examine such caregiver effects. Future studies with a larger sample of GCE children in non-kinship foster care will allow for much needed investigation of kinship versus non-kinship caregiver effects.

The difficulty of interpreting our null results is somewhat eased in the present case because of our ability to detect effects of age, child IQ, and aspects of earlier childhood experience (HOME composites) on NC function with the same cohort and task battery. According to Anastasi, the relation found here between the NC outcome and age at testing and IQ would be expected for any valid measure of cognitive function [3]. Further, using the NC task battery described here in an investigation of NC correlates of SES, we previously reported an overall SES effect as well as significant group differences (low vs. middle SES) in four of the NC systems [32].

Other investigations of the effect of GCE on cognitive abilities have found differences between cocaine exposed and non-exposed children after controlling for environmental factors known to be associated with cognitive outcomes [6,8,12,24,34,35,57,76,77]. While we were able to consider some of the variables commonly associated with poorer outcomes such as foster care placement, caregiver current cocaine use, and characteristics of the home environment, we did not have data on lead exposure or iron deficiency anemia, which have been shown in other studies to be associated with cognitive outcomes [77]. We also had limited data regarding amount and frequency of use of cigarettes, alcohol and marijuana during pregnancy. In some studies, environmental variables such as these have been reported to have a more powerful effect on a wider range of outcomes than gestational cocaine exposure [9,10,23,71,74]. Our findings notwithstanding, the effects of gestational cocaine exposure that have been identified by other researchers are not to be ignored as the clinical significance of those findings has not yet been determined.

Our results show a strong relation between early home environment and later NC outcome. This finding is consistent with other investigations of longitudinal effects of the home environment on child cognitive and academic outcomes [11,16,29,31,44,52,53,77]. As stated earlier, the HOME evaluations were completed twice, once at age 4 years and again at age 8 years. Our composite was computed using age 4 and 8 year home subscales, thus providing an average measure of the child's experience. NC testing was completed at age 12 years and it is likely that for some participants characteristics of the home environment may have changed both between and after these assessments. Bradley et al (2001) found that relations between characteristics of the home and cognitive and behavioral outcomes are stronger at younger ages, due to the increasing influence of other environments, such as school. We are limited in our ability to examine concurrent relationships between these types of variables at age 12 because we do not have measures of the home environment or measures of the quality of other environments, such as school at this time. Future studies are needed to examine the relative impact of current versus early home environment on outcomes. While it is true that prenatal exposures increase the risk for poorer outcomes, other variables such as characteristics of the home have significant short term and long term effects on cognitive outcome.

Statistically significant effects of prenatal exposure to cigarettes, alcohol and marijuana on cognitive outcome have reported by other researchers [22,37,46,57]. We show marginally significant effects of prenatal exposure to cigarettes and alcohol on NC outcome in Model 2 and 3 of our analyses. These effects did not remain when important covariates were added to the models due to small sample size and multicollinearity. In our cohort only two of the CGE children were not exposed to cigarettes during pregnancy and only two of the Control children were exposed to marijuana as shown in Table 1. Other studies of cocaine exposed children have shown this pattern of polysubstance exposure [5,30,77]. Interaction effects can not be reliably evaluated when cell sizes for these various subsets of the GCE and Control groups are so small. With a larger group of participants it is more likely that we would have been able to evaluate these interactions.

Our results may have been affected by the early attrition in our cohort. While analysis of differences in birth characteristics between subjects retained and those lost to follow up did

not reveal any differences in the measured variables, it may be that the children lost to follow-up are different in characteristics not measured, such as foster care placement or caregiver current cocaine use. It also is possible that with a higher retention we would have been able to examine non-kinship foster care effects in our cohort. As noted earlier, within the group of 120 included in this report only two were in non-kinship care, leaving too few subjects to evaluate the interesting effects reported by others [77].

The present results leave many questions unanswered, among them the reason for the discrepancy between the effects of GCE in humans and preclinical models. Furthermore, to the extent that our findings represent good news by suggesting that children with GCE may not experience NC impairments as a result of their exposure, the good news must be regarded as very tentative. We are tentative because some prenatal insults do not manifest themselves until maturity or later [36,63,78] as brain development in humans does not cease until at least the early twenties [20,41,42,59,69]. In fact, recent imaging analyses on this cohort show decreased volume in the caudate, a dopaminergically mediated brain area [4]. The possibility remains that the GCE and Control children of the present cohort may yet diverge in their NC development. Finally, the effects of GCE may be less apparent in simple protocols employing the assessment of cognitive function, such as the one used by us, than in more complex and stressful situations requiring the regulation of arousal and emotion along with cognitive performance [61]. For example, it may be that pairing a stress inducing protocol, such as the Trier Social Stress test [54] with a task of working memory [58,86], may reveal such an effect. Nevertheless, our results are informative in that they address NC functioning at one of the oldest ages so far reported in the GCE literature, and in that NC functioning was assessed by tasks that have been shown in other studies to engage specific NC systems. Replication of this type of investigation using a larger cohort of participants is needed to confirm our results. At present, results reported here both add support to the finding that GCE is not as potent a risk factor for child NC development as anticipated, as well as add to the literature identifying postnatal environmental factors as consistently potent influences on cognitive development.

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Abbreviations

BDI-II, Beck Depression Inventory - II
 CANTAB, Cambridge Neuropsychological Test Automated Battery
 FSIQ, Full Scale Intelligence Quotient
 GCE, Gestational Cocaine Exposure
 HOME, Home Observation for Measurement of the Environment
 ID/ED, Intra Dimensional / Extra Dimensional
 MANCOVA, Multivariate Analysis of Covariance
 MANOVA, Multivariate Analysis of Variance
 NC, Neurocognitive
 PPVT, Peabody Picture Vocabulary Test
 SES, Socioeconomic Status
 TROG, Test for the Reception of Grammar
 VOSP, Visual Object & Space Perception
 WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence – Revised Edition

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Table 1**Subject Characteristics by GCE Status**

	GCE (n = 55)	Control (n = 65)	p- value
At Time of Birth			
Gender, Female (n (%))	31 (56.4)	38 (58.5)	.95
Gestational Age, weeks (Mean ± SD)	37.6 ± 2.1	39.1 ± 2.0	<.001
Birth Weight, kg (Mean ± SD)	2.63 ± 0.51	3.15 ± 0.59	<.001
Birth Weight <10 th % ile for GA ^a	4 (7.3)	2 (3.1)	.29
Head Circumference, cm (Mean ± SD)	32.1 ± 1.7	33.5 ± 1.6	<.001
Head Circumference <10 th % ile for GA	9/54 (16.7)	3 (4.6)	.03
Race, African American	52 (94.5)	64 (98.5)	.23
Other Gestational Exposures			
Alcohol (n (%))	30 (54.5)	5 (7.7)	<.001
Marijuana (n (%))	25 (45.5)	2 (3.1)	<.001
Tobacco (n (%))	53 (96.4)	14 (21.5)	<.001
Gestational Cocaine Exposure, days (Median)	99	-	-
Maternal Age, years (Mean ± SD)	27.18 ± 4.3	22.4 ± 5.4	<.001
During School Years			
Age at NC testing, years (Mean ± SD)	12.3 ± 1.3	11.9 ± 1.2	.07
Wechsler Full Scale IQ at age 6 (Mean ± SD)	82.3 ± 13.6	82.6 ± 12.3	.91
Foster Care Placement (n (%))	26 (47.3)	8 (12.3)	<.001
HOME Score at age 4	40.3 ± 7.5	43.9 ± 5.4	.012
HOME Score at age 8	47.8 ± 5.1	49.2 ± 3.4	.095
Caregiver BDI-II Depression Score ^b	4	3	.26
Caregiver Current Cocaine Use (n (%))	30 (54.5)	5 (7.7)	<.001

^a GA= Gestational Age^b Range for the depression measure:0–40

Table 2

Neurocognitive Test Scores by GCE Status*

Neurocognitive Test	GCE	Control	Min	Max
Cognitive Control System				
Stroop Effect, msec	29.7 ± 18.0	28.3 ± 17.78	0	73
Go/No-Go, Total Correct (105 items)	96.5 ± 6.2	96.8 ± 5.1	79	104
Working Memory System				
2-Back, Total Correct (120 items)	108.5 ± 5.8	108.1 ± 6.1	94	118
Spatial Working Memory, Errors	48.8 ± 15.4	46.7 ± 17.3	9	79
Standard Score	93.4 ± 9.2	93.4 ± 11.3	65	123
Reward Processing System				
IED Shift Task, Total Errors Adjusted	47.8 ± 18.8	46.3 ± 19.2	9	76
Standard Score	94.6 ± 8.6	95.1 ± 8.3	79	112
Gordon Delay, Efficiency Ratio **	0.83 ± 0.15	0.86 ± 0.12	.50	1.00
Language System				
PPVT, Total Correct	119.2 ± 20.9	122.9 ± 22.2	82	168
Standard Score	83.5 ± 12.8	87.8 ± 13.8		
TROG, Total Correct	16.3 ± 2.2	16.4 ± 2.4	11	20
Standard Score	88.8 ± 14.5	90.9 ± 15.8	55	132
Memory System				
Visual Verbal, Recall Total Correct (80 items)	58.6 ± 7.9	60.1 ± 7.2	38	73
Faces, Recall Total Correct (80 items)	42.2 ± 6.1	44.0 ± 3.5	23	49
Spatial Cognition System				
Eckstrom Rotation, Total Correct (40 items)	30.7 ± 5.7	31.2 ± 5.8	18	40
Benton Line Orientation, Total Correct	30.1 ± 3.1	30.7 ± 2.9	23	36
Visual Cognition System				
Mooney Faces, Total Correct	28.8 ± 4.6	28.9 ± 4.7	16	35
VOSP, X-Detection, Total Correct **	19.1 ± 1.8	19.1 ± 1.4	12	20

* Using t-tests, with correction for Multiple Comparisons, all p-values were nonsignificant.

** This task was dropped from analysis.

Table 3
Relationships between Multivariate Neurocognitive Variable and Individual Covariates by MANOVA.

Covariates	Wilks Lambda p-values
Participant Characteristics at Birth	
Group (GCE/Control)	.532
Days of Gestational Cocaine Exposure	.68
Gender	.64
Gestational Age	.24
Birth Weight (BW)	.83
BW less than 10 th %ile	.62
Head Circumference (HC)	.74
HC less than 10 th %ile	.96
Maternal Characteristics at Delivery	
Maternal Age	.51
Maternal Gravida	.40
Gestational Exposure Variables	
Gestational Cigarette Exposure	.21
Gestational Alcohol Exposure	.037
Gestational Marijuana Exposure	.68
Participant Characteristics during Childhood	
Age at Neurocognitive Testing	.14
Characteristics of the Home Environment	
Parental Nurturance Composite	.017
Environmental Stimulation Composite	.53
Current Primary Caregiver Characteristics	
Caregiver Depression	.24
Caregiver Current Cocaine Use	.014
Foster Care Placement	.18

Table 4
MANCOVA Models with NC System Composite Scores as Dependent Variable – Multivariate p-values

Model	1	2	3	4	5
1 ^a					
GCE	0.37	0.47	0.46	0.24	-
Age at testing	-	0.004	<0.001	0.001	0.18
Gender	-	0.53 ^f	-	-	-
Prenatal Cigarettes	-	0.059	0.061	0.074	-
Prenatal Alcohol	-	0.045	0.16	-	-
Prenatal Marijuana	-	0.85	-	-	-
HOME: Environmental Stimulation	-	-	0.02	0.017	0.59
HOME: Parental Nurture	-	-	0.47	-	-
Any Foster Care	-	-	-	0.17	-
Caregiver Current Cocaine Use	-	-	-	0.11	-
Days of Gestational Cocaine Exposure (GCE group only)	-	-	-	-	0.46

^aModel Definitions: Intercept + GCE
^bIntercept + GCE + Age at testing + Gender + Prenatal Cigarettes + Prenatal Alcohol + Prenatal Marijuana
^cIntercept + GCE + Age at Testing + Gender + Prenatal Cigarettes + Prenatal Alcohol + HOME: Environmental stimulation + HOME: Parental Nurture
^dIntercept + GCE + Age at testing + Gender + Prenatal Cigarettes + HOME: Environmental stimulation + Any Foster Care + Caregiver Current Cocaine Use
^eIntercept + Age at testing + HOME: Environmental stimulation + Days of Gestational Cocaine Exposure
^fThere were no GCE by gender interactions (p=0.92).