J Youth Adolescence (2014) 43:53–69
DOI 10.1007/s10964-013-9927-3

EMPIRICAL RESEARCH

Comparison of 12-Year-Old Children with Prenatal Exposure to Cocaine and Non-Exposed Controls on Caregiver Ratings of Executive Function

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Received: 15 October 2012 / Accepted: 8 February 2013 / Published online: 20 February 2013
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Abstract Differences in caregiver reported executive function in 12-year-old children who were prenatally exposed to cocaine (PCE) compared to children who were not prenatally exposed to cocaine (NCE) were assessed. One hundred and sixty-nine PCE and 169 NCE, primarily African-American, low socioeconomic status children participated in a prospective longitudinal study. The Behavior Rating Inventory of Executive Function (BRIEF) Parent Form was administered. Two broadband BRIEF scores (Behavioral Regulation Index (BRI) and Metacognition Index (MI)) and a summary Global Executive Composite (GEC) were computed. Multiple and logistic regression analyses were used to assess the effects of amount of PCE on executive function, controlling for covariates including caregiver (rater) psychological distress, child's gender and other prenatal drug exposure variables. After adjustment for covariates, amount of PCE was associated with the GEC and two MI subscales, Plan/Organize and Monitor, with heavier exposure associated with more problems of executive function. An amount of PCE by gender interaction revealed amount of PCE effects in other remaining subscales of the MI (Initiate, Working Memory, and Organization of Materials) only among girls. Head circumference did not mediate the effects of cocaine on outcomes. Higher current caregiver psychological distress levels were independently associated with poorer ratings on the executive function scales. Assessment and targeted interventions to improve metacognitive processes are recommended for girls who were prenatally exposed to cocaine.

Keywords Executive function · Prenatal · Cocaine · BRIEF · Parental rating

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Introduction

At the height of the US crack cocaine epidemic of the late 1980s to the mid-1990s as many as 18 % of live births in some urban primarily low socioeconomic status areas were affected by prenatal exposure to cocaine (Kandel et al. 1998; Ostrea et al. 1992; SAMSHA 2000). Today rates of prenatal exposure to cocaine appear to have leveled off considerably in the US with 4.4 percent of pregnant women estimated to use any illicit drug (including but not limited to cocaine use) during 2009–2010 (SAMSHA 2011). The cumulative number of affected individuals raises concern for long term outcomes (Minnes et al. 2011; Ostrea et al. 1992). A growing body of research indicates that, while prenatal exposure to cocaine may not result in a reduction of general cognitive function (IQ) compared to control groups (Singer et al. 2008), it may increase the likelihood of behavioral and emotional regulation problems and be associated with more subtle neuropsychological difficulties

(Mayes and Fahy 2001; Richardson et al. 2011; Singer and Minnes 2004; Singer et al. 2008). However, the specific effects of prenatal exposure to cocaine on executive functioning (EF), a distinct grouping of higher order cognitive skills comprising working memory, response inhibition and set shifting, remains unclear. While there is considerable data regarding the developmental progression of EF throughout the lifespan, relatively little is known about the effect of fetal toxins on the development of executive function. Considering the large and steadily growing number of individuals affected by prenatal exposure to cocaine, the potentially additive negative effects of ongoing stress through poverty and substandard caregiving on the development of EF, and the critical role EF has in educational, vocational, and social achievements (Ylvisaker and Feeney 2002), the effects of prenatal exposure to cocaine on EF is an important area of study.

Effects of Prenatal Exposure to Cocaine on Fetal Brain Development

Maternal cocaine ingestion exerts a direct effect on the fetal brain as it passes through the placenta and the blood-brain barrier (Lee et al. 2008). In the brain, cocaine binds to monoaminergic transporters and prevents the uptake of extracellular monoamines into the presynaptic cells. Areas of the brain rich in monoamines (e.g. dopamine, serotonin and norepinephrine) are hypothesized to be the target of neuronal cell damage in fetuses exposed to cocaine (Malanga and Kosofsky 1999). More specifically, the prefrontal cortex and other higher order cortical areas that are rich in dopamine receptors are targets for cellular damage due to prenatal exposure to cocaine. The frontal cortex mediates cognitive processes of attention, planning, working memory and behavioral regulation (Thompson et al. 2009) and has been identified as one site of damage in animal studies of prenatal exposure to cocaine (Lidow 2003). Human brain imaging data, utilizing diffusion tensor imaging (DTI), supports this finding by showing underlying brain damage through greater frontal white matter diffusion (i.e. less mature development of frontal white matter pathways (Warner et al. 2006)) and lower total area of the corpus callosum (Dow-Edwards et al. 2006) in prenatally cocaine exposed compared to non-cocaine exposed children. Two other studies used functional magnetic resonance imaging (fMRI) and each assessed only one component of executive function. Hurt and colleagues (Hurt et al. 2008) found the cocaine exposed and non-cocaine exposed groups to be similar in performance on the n-back task (working memory) and fMRI activation patterns during task performance. A second fMRI study investigating another aspect of executive function (attention and response inhibition) found no difference in the go/no go behavioral task but differing levels of brain activation in the right inferior frontal cortex of exposed 8-9-year-old children compared to non-exposed children. Both studies are inconclusive regarding executive function, as they only assessed limited aspects of the neurocognitive domain, with small numbers of subjects (24 and 49), and lacked control for confounding variables. Other imaging studies did not directly interrogate frontal white matter tracts using DTI, did not focus on frontal functioning and/or used different imaging techniques (Liu et al. 2011).

Conceptualization and Measurement of Executive Function

Higher order cognitive processes, regulated by the prefrontal cortex, are often referred to as executive functions, since they encompass the ability to coordinate functions that control and direct thinking, behavior and emotional responses. They have been described as fluid and dynamic. Executive functioning is further defined as a set of regulatory processes necessary for goal directed behavior, including attending, selecting, initiating, implementing, and overseeing thought, emotion, behavior, and certain facets of motor and sensory function (Roth et al. 2005). Executive function is an important aspect of children's response to novel problem solving within their typical environments of school and home life. Therefore, executive function is vital for school success and social and emotional competence (McClelland et al. 2007; Shonkoff et al. 2000). Executive functioning is often called upon in context specific situations, including the home, classroom, or peer settings, posing measurement challenges and inconsistent results when using traditional clinical assessments such as neuropsychological or performance-based measures (Gioia et al. 2010). In addition to not being context sensitive, clinical assessments of executive function often tap into the individual components of executive function (e.g. working memory, inhibitory control, attention or set shifting) but fail to assess the overall or adaptive functioning.

Research has helped to define three related but distinct components of EF, including working memory, response inhibition, and cognitive flexibility/attentional set-shifting, with a central attention system serving as their foundation (Miyake et al. 2000). Using this model, Garon et al. (2008) reviewed the EF research conducted during early childhood and found that simple forms of core EF skills emerge early, and become developed and integrated during the preschool years. Blair and Ursache (Blair and Ursache 2011) propose a bidirectional model of EF and self-regulation that focuses on the interaction between cognition and emotion in the development of self-regulation. They propose that "top-down" executive control of thinking and behavior develops

in reciprocal and interactive relation to "bottom-up" automatic influences of emotion, attention and stress reactivity.

While there is a large body of research on the development of EF during the preschool years using traditional neuropsychological tasks that measure different EF components, less is known about the continued development of EF during school age and adolescence using tasks that vary in emotional or motivational significance. Prencipe et al. (Prencipe et al. 2011) examined EF in children between the ages of 8 and 15 years using a range of tasks varying in affective significance (i.e. "hot" vs. "cool" EF tasks) and found that while similar abilities may underlie both types of skills, hot or affectively charged EF develops more slowly and at later ages. Furthermore, these hot and cool components of executive function appear to have different developmental trajectories and therefore assessment tools need to be diverse in order to capture the wide range of executive functions and related behaviors.

Adverse rearing environments, particularly low income, low maternal education and insensitive/unresponsive parenting may negatively affect development of executive function in early childhood (Blair and Ursache 2011) and adolescence (Evans and Schamberg 2009). The negative impact that adverse environments can have on EF is largely attributable to the effect of poverty on stress physiology.

Association of Prenatal Exposure to Cocaine and Executive Function Performance

Neurobehavioral teratology researchers have investigated whether prenatal exposure to cocaine affects components of executive function in developing children. However, despite the complex issues of clinical measurement of executive function much of the research reports on highly specific subdomains of executive function.

Overall, there has been limited use of neuropsychological batteries to assess all three of the primary domains of executive function: working memory, inhibitory control, and set shifting, or to assess contextually sensitive caregiver or teacher reports of executive function. Among studies that have specifically explored the relationship between prenatal exposure to cocaine and executive function, direct and indirect effects of prenatal exposure to cocaine on one or more aspects of executive function have been found through the early elementary school years, with none reporting no association. In a small infant sample of 9.5- and 12.5-month-olds, prenatal exposure to cocaine was directly associated with poorer performance on the A-not-B task of executive function (Noland et al. 2003) after controlling for covariates. In a large preschool sample ($n = 308$), Eyler et al. (2009) found an indirect effect of fetal cocaine exposure through smaller head circumference on executive functioning skills measured by performance subscales of the WPPSI-R and WISC-III (Bock Design, Mazes and Coding) and the Hooper Visual Organization Test at ages 5 and 7. Importantly, this study also revealed that higher quality home environments, better caregiver functioning (less depression, and better locus of control and sense of parental competence) and being female also predicted better executive function performance, highlighting the need to control for environmental factors and evaluate effects of gender when examining executive function performance. Effects of prenatal exposure to cocaine have also been demonstrated at school age as well, with 9-year-old children performing more poorly than a control group on WISC-IV Perceptual Reasoning IQ (Block Design and Picture Concepts subscales (Wechsler 2003)) after control for environmental factors (Singer et al. 2008). While WISC Block Design and Picture Concepts subscales require some aspects of executive function, they have typically not been referred to as assessments of executive function per se and are likely an incomplete, only partial assessment of this type of skill.

Rose-Jacobs and colleagues (Rose-Jacobs et al. 2009) assessed two domains of executive function, i.e. verbal inhibitory control, and planning and organization. Their study emphasized the importance of using a measurement of the amount or level of cocaine exposure, as well as the absolute presence or absence (i.e. dichotomous variable) to predict executive function differences. In 9.5- and 11-year-old children, those who were most heavily cocaine exposed (defined as the top quartile of reported drug use per day during pregnancy and/or concentration of cocaine metabolites in infant meconium) performed more poorly on the Stroop Color-Word Test. However, there were no differences in performance between groups, regardless of level of exposure, on the Rey-Osterrieth Complex Figure Test, which assesses planning, organization and perception. The executive function assessments chosen by these researchers tap two distinct aspects of the executive function and fail to give meaningful results related to home and school functioning.

Consideration of Covariates

Prenatal exposures to alcohol (Burden et al. 2005) and marijuana (Fried and Smith 2001), and postnatal environmental variables such as caregiver psychological distress, caregiver cognitive functioning, and quality of the home environment, are also associated with poorer performance on cognitive tasks including executive function. Both higher rates of other prenatal drug exposures and lower quality postnatal environmental conditions occur at higher rates among prenatally cocaine/polydrug exposed children (Singer et al. 2002a; Singer and Minnes 2004) and should

be controlled in the investigation of executive function. In addition, elevated blood lead levels are associated with impairments in executive function (Chiodo et al. 2004; Singer et al. 2008; Trope et al. 2001) and also occur at high rates among high risk prenatally drug exposed children. Therefore, elevated lead levels should be considered as potential confounders. A considerable number of children exposed to cocaine prenatally are placed in foster or adoptive care, which can result in both higher quality home environments and lower blood lead levels, and should also be examined as a potential confounder.

Purpose of Study

The purpose of the present study was to examine executive function performance differences between preadolescent youth who had been prenatally exposed to cocaine and other drugs and youth who had not been prenatally exposed to cocaine using a caregiver report of executive function. A contextually sensitive measure of EF designed to assess overall, daily, academic and home life functioning among youth was employed. Addressing the behavioral regulation and metacognitive processes central to EF will provide an additional perspective that is lacking in the current literature. Caregiver report reflects day to day problems in the lives of youth rather than focusing on one or two clinical assessments that tap a discrete domain of executive function. It was hypothesized that youth prenatally exposed to cocaine would evidence more problems of executive functioning than youth not prenatally exposed, with greater levels of exposure related to more problems. Gender effects were also explored, as mental health and behavior problems specific to girls with prenatal exposure to cocaine have been found in this cohort (McLaughlin et al. 2011; Minnes et al. 2011).

Method

Participants

This study sample includes 338 12-year-old children (169 PCE and 169 NCE) recruited at birth for a longitudinal, prospective study (Singer et al. 2002a, b) investigating the developmental effects of prenatal exposure to cocaine. This sample is comprised of 84 % of the living original sample available for assessment. Mothers and their newborn infants were recruited from a large, urban, county teaching hospital with a high risk population screened for drug use. A nurse recruiter approached all screened women shortly before or after infant birth. Women received a urine drug screen if they reported to the medical staff that they had used cocaine or other drugs during pregnancy, appeared to be intoxicated at the time of delivery, did not receive prenatal care or had previous involvement with the Department of Children and Family Services. Children whose mothers had major confounding conditions including diagnosis of major depression, schizophrenia or bipolar disorder, low intellectual status (medical chart review indicated diagnosis of mental retardation), age < 19 years, positive HIV status or who were non-English speaking were excluded (54 mother/infant pairs). The exclusion criteria were discerned from documentation in the medical chart at the time of delivery. Four hundred fifteen mothers (218 PCE and 197 NCE) of the 647 mothers approached by a research nurse shortly after childbirth agreed to participate in the study. One hundred fifty-five women refused to participate (49 PCE and 106 NCE), and 23 (9 PCE, 14 NCE) did not come to the enrollment visit. Since birth, 12 children died (9 PCE and 3 NCE, $X^2 = 2.50$, $p = .11$). Causes of death for the cocaine exposed children were sudden infant death syndrome (4), cardiopulmonary arrest (1), pneumonia (1), accidental asphyxia (1), respiratory distress syndrome (1), and unknown illness (1). For the non-exposed children, causes of death were sudden infant death syndrome (2) and respiratory distress syndrome (1).

The PCE children who attended the 12-year follow up assessment had more average prenatal alcohol exposure ($p < .04$) but less average prenatal marijuana exposure ($p < .007$) than children who did not attend the assessment. NCE children who attended the 12-year assessment had less prenatal cigarette exposure ($p < .02$), higher birth weight ($p < .03$), longer birth length ($p < .003$) and fewer were small for gestational age ($p < .04$) than the NCE children who were not assessed.

Children were placed in the cocaine exposed (PCE) or non-cocaine exposed (NCE) groups based on maternal self-report of cocaine use during pregnancy to medical and/or research staff, biologic data collected from birth mothers (urine), and infant meconium screening. The Syva Emit method (Syva Co, Palo Alto, California) was used for urine analyses. Positive analyses were followed up by confirmatory gas chromatography. Infant meconium was collected from participating infants shortly after birth to further identify cocaine and other drug metabolites, including the presence of benzoylecgonine (BZE), meta-hydroxybenzoylecgonine (m-OH-bze), and cocaethylene, the major metabolites for cocaine, as well as other drugs of abuse including barbiturates, cannabinoids (THC), opiates, phencyclidine, amphetamines, and benzodiazepines. Identification of prenatal exposure to cocaine was based on positive results of maternal or infant urine, infant meconium or maternal interviews by hospital and research study staff. Of the 169 PCE children in this sample, 108 (63.9 %) were identified by both biologic (meconium and urine) and

self-report measures. Eleven (6.5 %) were determined by biologic measures only and 50 (29.6 %) were based on self-report only.

Procedures

Informed consent forms, approved by the participating hospital's Institutional Review Board (IRB), were reviewed with potential subjects by the research nurse and were signed by mothers. Maternal and infant birth data were extracted from the medical records and further maternal and infant assessments were scheduled to be completed within the first weeks after infant birth. A research assistant, blind to maternal cocaine use status, interviewed mothers about prenatal drug use. To quantify drug use during pregnancy, women were asked to recall frequency and amount of drug use during the month prior to becoming pregnant and during each trimester of pregnancy. The number of tobacco cigarettes and marijuana "joints" smoked and the number of drinks of beer, wine, or hard liquor per day were computed, with each drink equivalent to 0.5 oz. of absolute alcohol. For cocaine, the number of "rocks" consumed and/or the amount of money spent per day were noted and converted to a standard "unit" of cocaine. For each drug, frequency of use was recorded on a Likert-type scale ranging from 0 (not at all) to 7 (daily use), converted to reflect the average number of days per week a drug was used, except for cigarettes, which was collected as the number smoked per day. Frequency was multiplied by the amount used per day to compute an average use per week score for the month prior to pregnancy and for each trimester. The average use per week variable for each trimester and month prior was then averaged to obtain an average pregnancy use variable for each drug.

For the few individuals (10 from the entire sample) who did not self-report cocaine use during pregnancy but tested positive, an estimate of cocaine units per week value was assigned based on metabolite levels found in infant meconium screening completed at birth. This method is described in detail in another report (Arendt et al. 1999). Cocaine-positive infants were sub-divided into heavy and light categories. The heavy classification was determined by meconium screen or self-report indicating use greater than the 70th percentile for the cocaine users. For 10 women who denied cocaine use, but whose infants' meconium screens were positive, self-report data were estimated by assigning the median score for the group (heavy/light) to which they were assigned based on meconium status.

Assessment of continued drug use by caregivers was updated at each follow-up visit. Follow-up assessments of caregiver and child were conducted at ages 6, 12, and 18 months and 2, 4, and 9–12 years. Caregiver measures of receptive vocabulary and non-verbal reasoning were administered during the first year of the study and at the time of placement change up to 12 years.

At each assessment visit, caregivers signed the IRB approved, informed consent forms, and children signed an assent form. At the 12-year visit, a trained research assistant interviewed the child's current caregiver about current drug use and caregivers independently completed a rating of child executive function and self-report of psychological distress, among other measures. To reduce the potential for bias, a separate research assistant was used to administer the child assessment measures of the larger longitudinal study. Subjects were given a stipend of $100 ($50 each for caregiver and child) for the assessment. The primary measures used for this report are noted below.

Measures

Behavior Rating Inventory of Executive Function

The Behavior Rating Inventory of Executive Function (BRIEF) (Gioia et al. 2000) Parent Form for ages 5–18 years was completed at the 12-year assessment by the child's primary caregiver. It contains 86 items describing a child's behavioral functioning in the home under varying tasks and conditions in an effort to make it environmentally valid. Parents are asked to rate behavior as occurring never, sometimes, or often in the last 6 months (e.g. "Has trouble waiting for turn. Gets stuck on one topic or activity. Has explosive, angry outbursts. Has trouble getting through morning routine in getting ready for school."). These items yield 8 clinical scales including Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. Two additional scales were included to assess the reliability and accuracy of parental report: Inconsistency (acceptable if $\leq$6, questionable if 7 or 8, inconsistent if $\geq$9) and Negativity (acceptable if $\leq$4, elevated if 5 or 6, highly elevated if $\geq$7). No BRIEF caregiver report was found to be inconsistent or highly elevated. The clinical scales Inhibit, Shift and Emotional Control comprise the Behavioral Regulation Index (BRI) and the remaining five scales combine to form the Metacognition Index (MI). The formation of these two indices has been statistically supported in factor analysis (Gioia et al. 2000). Additionally, a Global Executive Composite summary score (GEC) is obtained based on the BRI and MI. A *T* score (adjusted for age and gender) greater than or equal to 65 (1 standard deviation above the mean of 50) indicates clinical concern, and is hypothesized to interfere with everyday functioning. For all BRIEF scales, a higher score indicates more difficulty with executive function related tasks. These scales have high levels

of reliability and validity, as well as adequate discriminant validity using clinical samples. Internal consistency ranges from .80 to .98 for Parent and Teacher forms and clinical and normative samples; mean test–retest correlation across clinical scales for a Parent Form normative sub-sample was r = .82 (range: .76–.88). The BRIEF correlates with other ratings scales of attention and behavioral functioning (ADHD Rating Scale IV, Child Behavior Checklist, Teacher Report Form, Behavior Assessment System for Children, and Conners' Rating Scales) and yields differing profiles of executive function with a variety of clinical groups hypothesized to evidence executive function deficits (e.g. ADHD, Traumatic Brain Injury, Tourette's Disorder, Pervasive Developmental Disorders). The Working Memory and Inhibit scales, in particular, exhibit predictive validity and clinical utility in detecting ADHD (Gioia et al. 2000). Studies have not demonstrated consistent correlations between the BRIEF and performance-based neuropsychological measures of executive function (Bodnar et al. 2007; McAuley et al. 2010; Vriezen and Pigott 2002). This may be because the BRIEF measures different aspects of executive function than those assessed by performance-based tests and/or that it is more sensitive to executive deficits in daily activities at home or in school compared to measures that are individually administered in a highly structured testing environment. Studies have found correlations between the BRIEF indices and measures of academic achievement in math and/or reading (Mahone et al. 2002; McAuley et al. 2010; Waber et al. 2006), although inconsistencies remain in terms of which indices are most predictive of math versus reading proficiency.

Demographics

Maternal and infant demographic and medical characteristics were collected from hospital birth records and included birth weight, height, head circumference, gestational age, race, maternal age, parity, and number of prenatal care visits. Data on occupation, years of education and number in family were collected via interview and a Hollingshead score was computed. Hollingshead scores of IV and V were used as indicators of low socioeconomic status (Hollingshead 1957).

Maternal Post-Partum Interview and Update

This semi-structured interview assessed amount and frequency of drug use during the month prior to and each trimester of pregnancy, and during the last 30 days at follow-up assessment. It included summary measures of average cigarette (per-day), alcohol, marijuana and cocaine (per-week) use over the pregnancy (Singer et al. 2002a; Streissguth 1986).

The amount and frequency of cocaine, tobacco, alcohol and marijuana used in the past 30 days was assessed again at each post-partum follow-up visit. Data from the Maternal Post-Partum Interview collected at birth and the 12-year visit were used in the current study.

Maternal/Current Caregiver Characteristics

Maternal and/or current caregiver receptive vocabulary was measured using the Peabody Picture Vocabulary Test-Revised (PPVT-R) (Dunn and Dunn 1981). Internal consistency of the PPVT-R ranges from .73 to .84, and test–retest reliabilities vary from .76 to .79. The PPVT-R is highly correlated with various measures of verbal IQ. Two subtests (Block Design and Picture Completion) of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler 1981) were also used to estimate non-verbal intelligence, as they correlate highest with Performance IQ (.81 and .75, respectively). Average (across age groups) split-half reliability coefficients for the WAIS-R Picture Completion and Block Design subtests are .81 and .87, respectively. Stability coefficients for Picture Completion range from .86 to .89 and from .80 to .91 for Block Design. The Global Severity Index (GSI) of the Brief Symptom Inventory (BSI) (Derogatis and Melisaratos 1983; Derogatis 1992) was used as a summary measure of psychological distress. The BSI is a 53-item self-report questionnaire. Scores on the GSI range from 0 to 4, with a clinical cutoff raw score of 1.19 or higher for women not referred for psychiatric illness. Reliability (α) of the BSI Global Severity Index (GSI), based on our data (Min et al. 2013) was .95. The Home Observation for Measurement of the Environment (HOME)—Early Adolescent version was administered to the caregiver in an interview format as a measure of the quality of the caregiving environment (Caldwell and Bradley 1984). Examples of items rated as present or absent in the home include, "Adolescent has access to desk or suitable place for reading or studying. Parent has read at least four books during past year. Parent teaches adolescent basic cooking or cleaning skills. Family has a fairly regular and predictable daily schedule. Adolescent eats at least one meal per day, on most days, with mother and father."

Child Measures

The WISC-IV (Wechsler 2003) Full Scale IQ measurement at age 11 was used as a control variable for the investigation of the effects of prenatal exposure to cocaine on executive function performance. The Assessment of Liability and Exposure to Substance Use and Antisocial Behavior© (ALEXSA©) (Ridenour et al. 2009), a computerized, child self-report that employs both visual and

auditory prompts related to substance use risk factors during childhood was completed at child ages 9, 10, 11, and 12 and evaluated as a potential covariate.

Blood Lead Level

At ages 2 and 4 years, all children attending the study assessment were asked to participate in a separate study of elevated blood lead and iron deficiency anemia. The numbers of subjects with valid blood measurements at ages 2 and 4 years were 143 and 274, respectively. For the 122 children with blood measurements at both times, the values were averaged. Blood samples could not be obtained from some children due to parental refusal, inability to draw blood without undue stress, child illness, or logistical difficulties. A greater percentage of African-American and married women and a lower percentage of foster parents consented to child blood collection. Elevated blood lead values were defined as $\geq$ 10 mg/dL at either age 2 or 4 years.

Statistical Analysis

Data that were positively skewed were normalized using a log transformation (prenatal drug exposure, GSI on the BSI, and lead) prior to analyses. Means and standard deviations are reported based on the original distribution but the test statistics are based on normalized data. Continuous data were compared by cocaine group status using t-tests or the Wilcoxon-Mann–Whitney test. Pearson Chi Square test or Fisher's Exact test were used for categorical variables. Analyses of Variance (ANOVA) were performed to compare executive function by cocaine status and gender. Significant overall tests were followed by post hoc tests using Tukey HSD adjustment. Multiple and logistic regression were used to assess the relationship between amount of PCE and executive function outcomes.

Covariates (prenatal alcohol, marijuana and tobacco exposure, maternal education, caregiver vocabulary ability, estimated non-verbal reasoning, current maternal and child drug use, child placement status, quality of the home environment, child IQ) correlated with the main dependent variables of the BRIEF at $p < .2$ and different by cocaine group status at $p < .2$, were evaluated in multivariate analyses. Caregiver psychological distress (GSI/BSI) was examined in every model first, after amount of PCE (average cocaine units per week) due to the consistent predictive value of maternal psychological distress when evaluating caregiver report of child behavior (Minnes et al. 2010; Pitzer et al. 2011; Suglia et al. 2011). Covariates were retained in the model if they were significant at $p \leq .10$ or changed the unstandardized regression estimate for cocaine by 10 %. Amount of cocaine exposure was considered a significant predictor if it was significant in the final model at $\leq$.05 (two-tailed test of significance).

After the main effects of amount of cocaine were evaluated, several follow-up analyses were conducted. If cocaine was associated with an executive function outcome, head circumference was evaluated as a mediator in follow-up analyses using Baron and Kenny's approach (Baron and Kenny 1986), as reduced head circumference may be one mechanism by which cocaine exposure may impact executive function (Bandstra et al. 2001; Eyler et al. 2009). Previous research in our laboratory found that amount of PCE predicted head circumference in this cohort at birth (Singer et al. 2000). Cocaine by gender interaction was evaluated in all models and results were presented if the interaction was significant at $p \leq .05$. Current caregiver type (PCE biologic/relative, PCE foster/adoptive care and NCE) was also assessed to determine if there were additional associations based on child placement. Due to the reduced sample size, the effects of blood lead level at 2 and/or 4 years of age were evaluated last to examine additive or confounding effects of lead exposure.

Results

Child and Caregiver Characteristics

Adjusted for gestational age, children with PCE were more likely to have had lower birth weight, length, and head circumference than NCE children (see Table 1). Children with PCE were also more likely to be microcephalic, small for gestational age and in adoptive or foster care at age 12 years (all p's $< .001$). There was a trend for differences in lead level by group, with NCE children having higher blood lead at 2 and/or 4 years ($p < .06$). Participants were not different on Hobel Risk scores at birth, the percent African-American, chronological age, and average HOME scores at age 12.

Birth mothers of PCE children were older, had more children, and had significantly more psychological distress at the time of infant birth (p's $< .0001$) than mothers of NCE children (see Table 2). Cocaine-using women also had fewer years of education, poorer receptive vocabulary skills, less prenatal care (p's $< .002$) and were less likely to be married ($p < .02$) than non-cocaine using women. Cocaine using women also consumed more cigarettes per day, and more drinks and marijuana joints per week on average during the prenatal period than non-cocaine using women. For cocaine-using women, the average prenatal cocaine use was 23.49 (SD = 39.61) units per week. Cocaine use during the month prior to pregnancy was 31.79 units per week. Cocaine use in the first trimester was 32.18 units per week, 24.77 units per week in the second

Table 1 Child demographics

Child demographics	Cocaine (n = 169)		Non-cocaine (n = 169)		*p*
	M	SD	M	SD	
1 min Apgar	8.00	1.46	7.90	1.72	.56
5 min Apgar	8.78	0.65	8.76	0.73	.79
Gestational age	37.94	2.77	38.47	2.95	.09
Hobel neonatal risk score	6.89	15.81	6.14	16.37	.67
Birth length (cm)*	47.56	3.89	49.23	3.76	<.0001
Head circumference (cm)*	32.42	2.12	33.48	2.95	<.0001
Birth weight (grams)*	2,751	633	3,116	712	<.0001
Male, n (%)	76	44.97	80	47.34	.66
African-American, n (%)	138	81.66	136	80.47	.78
Microcephaly, n (%)	24	14.29	7	4.19	.001
Small for gestational age, n (%)	21	12.57	2	1.19	<.0001
2 and/or 4 years Lead level[a]	6.92	4.11	7.87	4.51	.06
11 years IQ score	84.18	13.06	87.25	13.85	.04
Any drug use[b], n (%)	44	28.95	50	33.56	.39
Adopted/foster care at 12 years, n (%)	38	22.49	6	3.55	<.0001
Test age	12.07	0.27	12.11	0.24	.18

* *p* value is adjusted for prematurity

[a] Sub-sample size of lead is 263, included 131 PCE and 132 NCE

[b] Lifetime any drug use (Yes/No). Summarized from ALEXSA at 9–12 years old

trimester, and 11.22 units per week in the third trimester. Among women who used cocaine during pregnancy, there were 100 (out of 120 who responded, 83 %) cocaine-using women who reported that crack cocaine was their form of choice in the month prior to pregnancy. There were 94 (out of 114 who responded, 82 %) cocaine-using women who reported that crack cocaine was their form of choice in the first trimester, 84 (out of 97 who responded, 87 %) cocaine-using women who reported that crack cocaine was their form of choice in the second trimester, and 92 (out of 108 who responded, 85 %) cocaine-using women who reported that crack cocaine was their form of choice in the third trimester. An examination of current caregivers demographic variables and drug use habits at age 12 by group revealed that the current caregivers of children with PCE had less education and smoked more cigarettes per day (p's $< .05$) than the current caregivers of NCE children.

Effects of Prenatal Exposure to Cocaine on Caregiver Rated Executive Function

Average unadjusted caregiver ratings on all BRIEF summary scores (Behavioral Regulation Index, Metacognition Index, and Global Executive Composite) by cocaine status and gender indicated overall group differences. The differences were primarily between girls with PCE having higher, or more problematic, average BRIEF scores compared to non-cocaine exposed girls (p's $< .05$) (See Table 3). In addition, the majority of BRIEF subscales were statistically higher for girls with PCE compared to NCE girls (p's $< .05$), with the exception of Organization of Materials, in which there was no difference.

Table 4 indicates that after adjustment for covariates, amount of PCE was associated with the GEC ($\beta = .13$; $p < .02$) and two subscales of the MI, Plan/Organize ($\beta = .15$; $p < .02$) and Monitor ($\beta = .15$; $p < .009$). Evaluation of the amount of PCE by gender interaction revealed significant associations with MI ($\beta = .26$; $p < .0008$) and three subscales of MI: Initiate ($\beta = .23$; $p < .005$), Working Memory ($\beta = .27$; $p < .0006$) and Organization of Materials ($\beta = .27$; $p < .001$) for PCE females only. Figure 1 provides a graphic representation of the negative effects of higher levels of prenatal exposure to cocaine on problems of metacognitive ability among girls compared to boys. Foster/adoptive care placement status was evaluated in each model that indicated an effect of amount of PCE on problems of executive function. However, no significant adoptive or foster care placement associations were observed. Also, head circumference did

Table 2 Maternal and current caregiver characteristics

Demographics	Cocaine (n = 169)		Non-cocaine (n = 169)		*p*
	M	SD	M	SD	
Maternal (prenatal/post-natal)					
Mother's age at birth	29.75	5.02	25.67	4.66	<.0001
Parity	3.53	1.90	2.68	1.85	<.0001
Number of prenatal visits	5.28	4.66	8.86	4.86	<.0001
Maternal years of education	11.47	1.55	12.02	1.42	.0009
PPVT standard score	72.99	14.46	78.10	14.56	.002
WAIS-R Block Design	6.89	2.12	7.16	2.05	.25
WAIS-R Picture Completion	6.68	2.13	6.93	2.37	.31
Global Severity Index	0.82	0.75	0.51	0.54	<.0001
Married, n (%)	13	7.69	27	15.98	.02
Low SES, n (%)	165	98.21	165	97.63	.71
African-American, n (%)	139	82.25	137	81.07	.78
Prenatal cigarettes per day[a]	11.77	10.28	3.85	7.32	<.0001
Prenatal drinks per week[b]	10.28	17.90	1.07	3.15	<.0001
Prenatal marijuana per week[c]	0.92	2.67	0.65	3.65	.002
Prenatal cocaine units per week[d]	23.49	39.61	–	–	NA
Month prior cocaine per week[d]	31.79	60.54	–	–	NA
1st Trimester cocaine per week[d]	32.18	64.49	–	–	NA
2nd Trimester cocaine per week[d]	24.77	62.35	–	–	NA
3rd Trimester cocaine per week[d]	11.22	24.56	–	–	NA
Current caregiver (at the 12-year assessment)					
HOME score at 12 years	48.04	6.79	49.09	6.18	.13
Years of education	11.99	2.40	12.83	1.89	.0004
PPVT standard score	79.07	15.03	79.80	15.62	.67
WAIS-R Block Design	7.13	2.16	7.32	1.93	.39
WAIS-R Picture Completion	7.44	2.64	7.16	2.36	.32
Global Severity Index	0.35	0.44	0.36	0.49	.82
Cigarettes per day[a]	5.51	7.77	4.00	6.88	.04
Drinks per week[b]	1.23	3.07	1.25	3.15	.98
Marijuana joints per week[c]	0.94	7.33	0.11	1.11	.16

[a] Average number of cigarettes smoked per day

[b] Average drinks of beer, wine, or hard liquor per week, each equivalent to .5 mL absolute alcohol

[c] Average joints of marijuana per week

[d] Average units of cocaine units per week

not mediate the effects of cocaine on any of the BRIEF scores, nor did it have an independent or additive effect on executive functioning performance.

Evaluation of adjusted BRIEF outcomes by clinical cut off scores (clinical problems (T-score $\geq$ 65) versus average range (T-score < 65)) using logistic regression, controlling for covariates, indicated several significant effects for PCE girls only, with increasing levels of prenatal exposure to cocaine predicting higher rates of clinically significant problems with executive function (Table 5). More heavily cocaine exposed girls were more likely to have clinically elevated MI (OR = 1.34, CI: 1.05–1.71, $p < .02$) and GEC (OR = 1.70, CI: 1.27–2.29, $p < .0004$). In addition two subscales of MI, Working Memory (OR = 1.34, CI: 1.04–1.73, $p < .03$) and Organization of Materials (OR = 1.58, CI: 1.13–2.19, $p < .007$) and a subscale of BRI, Inhibit (OR = 1.54, CI: 1.16–2.04, $p < .003$) indicated higher likelihood of clinically elevated scores among girls with higher amounts of prenatal exposure to cocaine. Adjusted percentages for clinically elevated executive function problems for PCE versus NCE girls were as follows: MI (24.66 % vs.13.48 %), GEC

Table 3 Unadjusted BRIEF mean T-score by gender and cocaine group status

	Boys (n = 156)				Girls (n = 182)				F^e	p
	PCE (n = 76)		NCE (n = 80)		PCE (n = 93)		NCE (n = 89)			
	M	SD	M	SD	M	SD	M	SD		
Behavioral Regulation[a,b,c]	56.42	13.59	55.70	14.19	55.84	11.63	49.63	9.92	5.82	.0007
Inhibit[a,b,c]	57.91	12.50	57.31	12.55	58.42	12.18	51.94	9.47	5.81	.0007
Shift[a]	53.28	12.07	53.03	13.84	55.12	11.16	49.12	10.30	4.07	.007
Emotional Control[a,c]	54.51	12.94	53.85	13.50	52.22	10.86	47.73	9.90	5.70	.0008
Metacognition[a]	53.16	9.50	53.20	10.52	56.86	11.92	50.08	10.84	5.98	.0006
Initiate[a,c]	51.87	8.74	52.74	9.57	55.42	10.49	48.90	9.43	7.05	.0001
Working Memory[a,d]	54.45	9.24	54.99	11.66	59.10	11.72	52.27	11.90	5.86	.0007
Plan/Organize[a]	53.60	9.70	53.28	10.39	57.26	12.13	50.97	10.95	5.19	.002
Organization of Materials	49.91	8.68	49.69	9.95	51.95	10.65	48.61	9.78	1.82	.14
Monitor[a]	53.17	11.17	52.16	10.51	56.14	11.70	49.36	10.17	5.97	.0006
Global Executive Composite[a]	54.56	11.32	54.30	12.22	56.98	12.12	49.97	10.51	5.72	.0008

[a] Significant difference between girls with PCE and girls with NCE

[b] Significant difference between boys with PCE and girls with NCE

[c] Significant difference between boys with NCE and girls with NCE

[d] Significant difference between boys with PCE and girls with PCE

[e] $df = 3, 334$

Table 4 Adjusted association of BRIEF T-scores with amount of cocaine

	Whole				Boys				Girls			
	β	b (SE)	t	p	β	b (SE)	t	p	β	b (SE)	t	p
Behavioral Regulation[a]	.06	0.49 (0.53)	0.92	.36		–				–		
Inhibit[b]	.07	0.57 (0.52)	1.10	.27		–				–		
Shift[c]	.07	0.54 (0.46)	1.17	.24		–				–		
Emotional Control[d]	.04	0.32 (0.45)	0.72	.47		–				–		
Metacognition[e]		–			−.001	−0.01 (0.61)	−0.01	.99	.26	2.03 (0.60)	3.40	.0008
Initiate[f]		–			−.11	−0.67 (0.58)	−1.15	.25	.23	1.61 (0.56)	2.87	.005
Working Memory[g]		–			.01	0.05 (0.65)	0.08	.94	.27	2.17 (0.62)	3.50	.0006
Plan/organize[h]	.15	1.08 (0.47)	2.28	.02		–				–		
Organization of Materials[i]		–			.04	0.26 (0.58)	0.45	.65	.27	1.87 (0.57)	3.29	.001
Monitor[j]	.15	1.13 (0.43)	2.61	.009		–				–		
Global Executive Composite[k]	.13	1.04 (0.45)	2.30	.02		–				–		

Covariates adjusted for in each model are listed below. Significant covariates are italicized

[a] *Current caregiver GSI score,* prenatal average cigarette exposure and prenatal average alcohol exposure

[b] *Current caregiver GSI score,* maternal education, prenatal average cigarette exposure and prenatal average alcohol exposure

[c] *Current caregiver GSI score*, HOME score and prenatal average cigarette exposure

[d] *Current caregiver GSI score,* HOME score, prenatal average cigarette exposure and *sex*

[e] *Current caregiver GSI score* and prenatal average cigarette exposure

[f] *Current caregiver GSI score,* prenatal average cigarette exposure and prenatal alcohol month prior exposure

[g] *Current caregiver GSI score,* maternal education and prenatal average cigarette exposure

[h] *Current caregiver GSI score,* prenatal average cigarette exposure and prenatal average alcohol exposure

[i] *Current caregiver GSI score,* maternal marital status, *maternal PPVT score* and prenatal average cigarette exposure

[j] *Current caregiver GSI score* and *prenatal average cigarette exposure*

[k] *Current caregiver GSI score* and prenatal average cigarette exposure

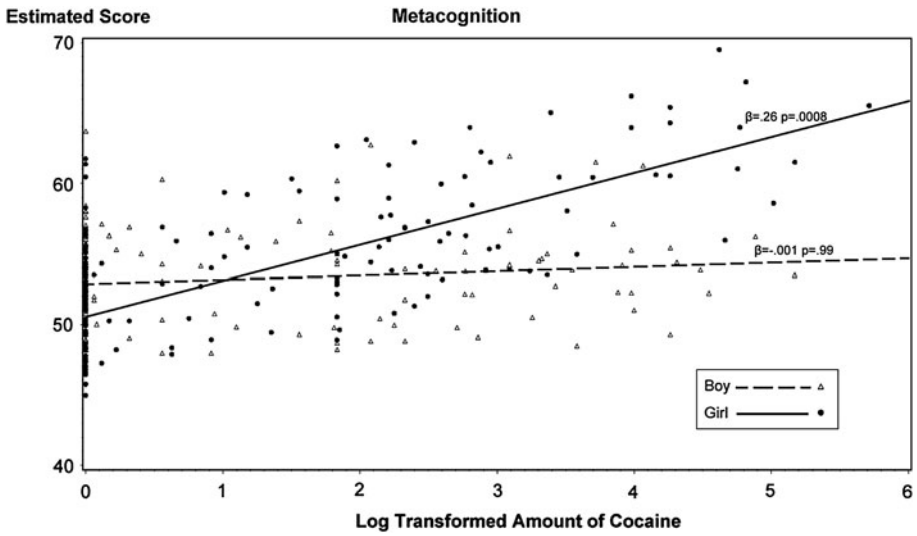

Fig. 1 Amount of cocaine and gender interaction for BRIEF metacognition T score

Table 5 Adjusted odds of clinically significant BRIEF scores by amount of prenatal exposure to cocaine

T-score ≥ 65 (yes/no)	Whole		Boys		Girls	
	OR (95 %)	*p*	OR (95 %)	*p*	OR (95 %)	*p*
Behavioral Regulation[a]	1.06 (0.86, 1.31)	.58	–	–	–	–
Inhibit[b]	–	–	0.90 (0.64, 1.25)	.52	1.54 (1.16, 2.04)	.003
Shift[c]	1.09 (0.93, 1.01)	.40	–	–	–	–
Emotional Control[d]	1.06 (0.85, 1.32)	.59	–	–	–	–
Metacognition[e]	–	–	1.06 (0.53, 2.13)	.87	1.34 (1.05, 1.71)	.02
Initiate[f]	1.07 (0.84, 1.36)	.58	–	–	–	–
Working Memory[g]	–	–	0.80 (0.53, 1.21)	.29	1.34 (1.04, 1.73)	.03
Plan/organize[h]	1.22 (0.97, 1.54)	.10	–	–	–	–
Organization of Materials[i]	–	–	0.84 (0.53, 1.35)	.48	1.58 (1.13, 2.19)	.007
Monitor[j]	1.18 (0.93, 1.50)	.17	–	–	–	–
Global Executive Composite[k]	–	–	0.83 (0.61, 1.14)	.25	1.70 (1.27, 2.29)	.0004

Covariates adjusted for in each model are listed below. Significant covariates are italicized

[a] *Current caregiver GSI score,* prenatal average cigarette exposure and prenatal average alcohol exposure

[b] *Current caregiver GSI score,* maternal education, prenatal average cigarette exposure and prenatal average alcohol exposure

[c] *Current caregiver GSI score*, HOME score and prenatal average cigarette exposure

[d] *Current caregiver GSI score,* HOME score, prenatal average cigarette exposure and *sex*

[e] *Current caregiver GSI score* and prenatal average cigarette exposure

[f] *Current caregiver GSI score,* prenatal average cigarette exposure and prenatal alcohol month prior exposure

[g] *Current caregiver GSI score,* maternal education and prenatal average cigarette exposure

[h] *Current caregiver GSI score,* prenatal average cigarette exposure and prenatal average alcohol exposure

[i] Current caregiver GSI score, maternal marital status, maternal PPVT score and prenatal average cigarette exposure

[j] Current caregiver GSI score and *prenatal average cigarette exposure*

[k] *Current caregiver GSI score* and average prenatal cigarette exposure

(26.46 % vs. 9.09 %) and Inhibit (29.39 % vs. 13.22 %), Working Memory (34.81 % vs. 20.75 %) and Organization of Materials (18.13 % vs. 5.60 %).

Other Predictors of Caregiver Rated Executive Function Problems

For all BRIEF mean summary and subscale T-scores, higher current caregiver psychological distress levels were independently associated with increased ratings of executive function problems (p's $< .05$). The only other prenatal drug exposure that had a significant independent effect on caregiver rating of executive function was average prenatal cigarette exposure, which was associated with more problems on the Monitor Scale ($\beta = .12$; $p < .04$). Lower maternal receptive vocabulary scores were associated with more Organization of Materials problems ($\beta = .14$; $p < .01$). There were no significant associations of prenatal alcohol or marijuana exposure with problems of executive function.

Blood lead level at 2 and/or 4 years of age was not a significant independent predictor of any of the BRIEF summary or subscale scores, although there was a trend for an association with 2 MI subscales, Organization of Materials ($p < .07$) and Monitor ($p < .08$). Youth self-reported drug use between the ages of 9–11 years was assessed in each model and there were no associations. However, when Full Scale IQ was assessed in each model it was a significant independent predictor of executive function performance (p's $< .05$) but did not change the relationship between amount of PCE and BRIEF summary scores or subscales.

Discussion

Executive function is increasingly viewed as a complex set of distinct but related higher order cognitive processes that are critical for educational, vocational, and social success across the lifespan. Given the multidimensional nature of the EF concept, multiple ways of measuring the various components of executive function have been developed for different ages, under varying conditions, using typical and atypical groups. The components of EF appear to have different developmental trajectories, and biological and environmental factors may alter those trajectories. Adding to the complexity, performance-based tasks of EF do not always correlate with more ecologically sensitive measures. Hughes (2011) provides a thorough review of the developmental research on EF and its many challenges.

The current study focused on the effect of prenatal exposure to cocaine on executive function. Executive function was measured using an ecologically sensitive, caregiver questionnaire of skills manifested in everyday behaviors at home, including those in relation to school activities. The results of the present study provided support for our hypothesis that youth with prenatal exposure to cocaine evidenced more problems in executive function, as reported by their caregivers, than non-exposed youth. Additionally, a dose–response relationship was present, with greater levels of cocaine exposure related to higher levels of reported executive dysfunction. However, the findings were largely gender dependent. After control for covariates, higher amounts of prenatal exposure to cocaine were associated with higher rates of both average T-scores and clinically elevated problems of executive function, particularly in metacognition, for females but not males. Head circumference did not mediate these effects. Greater prenatal exposure to cocaine in girls was associated with more problems with initiation of activities and generation of ideas (Initiate), holding information in mind for the purpose of completing a task (Working Memory) and establishing order while carrying out an activity in a systematic manner (Organization of Materials). Adjusted percentages of PCE girls with clinically elevated BRIEF scores indicated alarmingly high rates of executive function problems, ranging from 18 % in Organization of Materials to 35 % in Working Memory. Higher levels of prenatal exposure to cocaine were also associated with higher odds of having overall executive function problems (26.46 vs. 9.09 %; Global Executive Composite) in PCE but not NCE girls. Interestingly, there were no effects of prenatal exposure to cocaine on executive function specifically in boys in our sample.

Higher current caregiver level of psychological distress was consistently related to higher problem scores on the BRIEF. This finding is consistent with other measures of parental ratings of problem behavior in children from this study cohort (McLaughlin et al. 2011; Minnes et al. 2010) and the research literature in general (Youngstrom et al. 1999). Levels of blood lead, prenatal exposure to alcohol, and prenatal exposure to marijuana were not independently related to more problems in executive function in this sample. This finding suggests a unique negative effect of prenatal exposure to cocaine on executive function at 12 years, particularly among exposed females.

The present findings are corroborated by research that has demonstrated that maternal cocaine ingestion exerts direct negative effects on the fetal brain (Lee et al. 2008) and that areas of the brain rich in monoamines (e.g. dopamine, serotonin and norepinephrine) are the targets of neuronal cell damage (Malanga and Kosofsky 1999). More specifically, deficits in executive function reported by caregivers indicate problems associated with the prefrontal cortex, which mediates cognitive processes such as attention, planning, working memory and behavioral regulation

(Lidow 2003; Thompson et al. 2009). Human brain imaging data has also suggested underlying brain damage, due to prenatal exposure to cocaine through greater frontal white matter diffusion (i.e. less mature development of frontal white matter pathways (Warner et al. 2006)) and lower total area of the corpus callosum (Dow-Edwards et al. 2006). While the negative effect of amount of PCE is evident in some cases for the whole group (BRIEF Global Executive Composite, Monitor and Plan/Organize subscales T-scores), the Metacognition Index and three of its subscales (Initiate, Working Memory, and Organization of Materials) were significant for females only. These findings are consistent with other results from our sample showing greater sensitivity among females to the effects of prenatal exposure to cocaine on caregiver reported behavioral ratings using the Child Behavior Checklist at age 9 (McLaughlin et al. 2011) and longitudinally from 6 to 10 years (Minnes et al. 2010). However, other studies of behavior and executive function among children prenatally exposed to cocaine have suggested that being female was a protective factor (Eyler et al. 2009), and have found that males had more negative behavioral outcomes (Bennett et al. 2007; Carmody et al. 2011; Delaney-Black et al. 2004). It has been suggested that while males exposed prenatally to cocaine appear more vulnerable than females across the neurobehavioral spectrum, it may be that females have been given much less attention in the literature (Williams et al. 2011).

Despite the benefits of using the BRIEF, researchers have not found it to be consistently correlated with clinical measures of executive function. This is likely due to the fact that many clinical assessments tap only one domain of executive function at a time and therefore several different measures must be used for clinical assessment. In addition, clinical assessments are administered in highly controlled conditions rather than context sensitive ratings of executive function as observed in everyday settings such as home or school (Gioia et al. 2010). When the results of this study are compared with other studies employing clinical assessments of executive function, findings are fairly consistent and add a unique dimension. Eyler and colleagues (Eyler et al. 2009) found an indirect effect of prenatal exposure to cocaine through head circumference on poorer performance on the WPPSI and WISC-III Block Design in 5- and 7-year-old children. However, while the Eyler study (Eyler et al. 2009) indicated that the relationship was mediated by head circumference, the present study did not find the same mediation effects. In addition, direct effects of cocaine on the WISC-IV Block Design subtest and Perceptual Reasoning Index were found by Singer et al. (2008) at age 9 and provide some evidence of consistency in the sample. Rose-Jacobs et al. (2009) reported an association of heavier cocaine exposure in 9.5- and 11-year-old children with some aspects of executive function (inhibitory control but not planning and organization), which is consistent with the findings of the present study.

To our knowledge this study is the first known to use a context sensitive, parent report of executive function to evaluate the effect of prenatal exposure to cocaine on executive function, controlling for numerous confounding factors. The BRIEF captures information about executive function problems in everyday behaviors that occur at home, school and in the community. This type of contextual report is thought to be a very useful source of information to access when developing individualized treatment plans (Gioia et al. 2010). However, it has also been found that caregiver reports can be quite sensitive to rater bias as the information is filtered through another individual whose response is dependent on their own cognitive and psychological status (Youngstrom et al. 1999). Current caregiver psychological status was controlled for in each model and this weakness was addressed statistically.

These data indicate that 12-year-old females with prenatal exposure to cocaine display more problems of executive function in their daily life at home and in school related activities, as reported by their caregivers, compared to other high risk, polydrug, but non-cocaine exposed females. Aspects of daily functioning that appear to be affected would include initiating, planning, and organizing tasks, sustaining working memory, and monitoring one's performance. Given the high percentage of PCE girls with clinical elevations on both the Working Memory and Inhibit subscales, it would be predicted that more children who were prenatally exposed to cocaine would present at school age with problems of inattention and impulsivity (i.e. ADHD) that might require more interventions compared to children non-exposed.

Adaptive behaviors at home and in academic settings that are influenced by executive function should be the target of early and sustained educational interventions for children at risk, such as those with prenatal exposure to cocaine. Interventions should be developed that involve both the teacher and caregiver to ensure that ecologically relevant concerns are targeted for improvement. Executive function skills are strongly associated with school readiness (Diamond and Lee 2011). Therefore, early intervention programs for socioeconomically disadvantaged preschoolers have been designed to teach cognitive control skills as part of the regular classroom curriculum (Bierman et al. 2008; Diamond et al. 2007). Riggs et al. (2006) have identified executive function as a key element in the development of social-emotional skills during elementary school and suggest that all school-based interventions aimed at promoting social-emotional competence include some assessment and enhancement of basic executive functioning.

The study's reliance on caregiver report of executive function is both a strength and weakness. Future studies

should include data from additional, corroborative sources such as teachers, the child's self-report, and a comprehensive clinical assessment of executive functions. The study would also be strengthened if executive function could be evaluated within a developmental trajectory by examining repeated measures of the BRIEF across early childhood and adolescence. There is some indication that executive functions continue to develop during the adolescent years and the rate of development may be impacted by stage of pubertal development (Steinberg 2005). Future studies that investigate executive function during later adolescence, should consider stage and onset of pubertal development. Finally, the sample was recruited at delivery and as such recall bias may affect the caregiver's ability to accurately recall early pregnancy substance use. The generalizability of results is limited to high risk, urban, primarily African-American samples.

Additional strengths of this study are the collection of data within the context of an ongoing longitudinal, prospectively designed, and well-characterized sample. The use of an ecologically sensitive measure of executive function contributes to the overall understanding of the needs of children with prenatal exposure to cocaine in their everyday environment in a way that other studies do not. This study sample from which the data is drawn is a significant strength, with over 90 % of the sample retained at the 12-year assessment. In addition, the study controlled for a large number of potentially confounding variables, including those known to impact executive function such as prenatal alcohol exposure and indicators of poverty and stress in the environment. Other important potential confounding variables, including placement in foster or adoptive care and substance use by the child, were evaluated although not found to be significant predictors of executive function. It is possible that these variables may be mediated through maternal psychological distress and other factors influencing the quality of the home environment.

Conclusion

Twelve-year-old children with higher amounts of prenatal exposure to cocaine were rated by caregivers as having more overall problems of executive function. This finding adds to the existing but sometimes inconsistent literature using clinical assessments of executive function in children with prenatal exposure to cocaine. In particular, females with prenatal exposure to cocaine had greater problems with initiating activities, working memory and organization compared to girls not exposed to cocaine prenatally. As many developing skills require executive function for success, health professionals should consistently screen children with prenatal exposure to cocaine for functional problems that interfere with home and school life. Educational interventions that promote the development of executive function skills should be incorporated into early childhood and elementary school programs for at-risk children.

Acknowledgments We wish to thank all of our families who participated in our research. We would also like to thank Laurie Ellison and Paul Weishampel for research assistance and Terri Lotz-Ganley for manuscript preparation. This research was supported by a National Institute on Drug Abuse Grant R01-07957.

Author contributions SM participated in the study's conception, design, coordination, statistical analyses, interpretation of the data, and drafted the manuscript; LS participated in the study's conception and design, interpretation of data, and helped to draft the manuscript; MM performed the statistical analyses, participated in the interpretation of data, and helped to draft the manuscript; AL participated in the coordination of the study, performed the measurements, and helped to draft the manuscript; ABH participated in the initial literature review and draft of the manuscript; ES participated in the study's conception, design and interpretation of the data, and helped to draft the manuscript; MW provided data management, performed statistical analyses, participated in interpretation of data, and helped to draft the manuscript. All authors read and approved the final manuscript.

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