Drug and Alcohol Dependence 177 (2017) 93–100

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Association of prenatal cocaine exposure, childhood maltreatment, and responses to stress in adolescence

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ARTICLE INFO

Keywords:
Prenatal cocaine exposure
Childhood maltreatment
Stress response
Coping
Adolescents

ABSTRACT

Background: Prenatal cocaine exposure (PCE) may alter responses to stress. Children with PCE tend to grow up in suboptimal caregiving environments, conducive to child maltreatment (CM). Guided by the diathesis-stress model, the present study examined differences in self-reported responses to stress and coping in adolescents with and without PCE and explored whether childhood maltreatment (CM) moderated the effects of PCE.

Methods: Adolescents (N = 363; 184 PCE, 179 non-cocaine exposed (NCE)), primarily African-American and of low socioeconomic status, were prospectively enrolled in a longitudinal study at birth. The Responses to Stress Questionnaire was used to assess volitional coping (primary control, secondary control, disengagement) and involuntary responses (involuntary engagement, involuntary disengagement) to stress at the 15- and 17-year follow-up visits. CM was assessed retrospectively at age 17 using the Juvenile Victimization Questionnaire.

Results: Findings from longitudinal mixed model analyses indicated that PCE was associated with poorer coping strategies only among adolescents with a history of CM. Adolescents with PCE who experienced CM reported less dominant use of primary (e.g., problem solving, emotional regulation) and secondary control (e.g., cognitive restructuring) and more dominant use of disengagement (e.g., denial, avoidance) and involuntary disengagement (e.g., inaction) than adolescents with PCE who did not experience CM or NCE adolescents regardless of CM. CM was associated with more dominant use of involuntary engagement (e.g., intrusive thoughts).

Conclusions: PCE may increase sensitivity to CM, predisposing increased vulnerability to environmental risk. Continued studies into adulthood will elucidate how coping and involuntary stress responses affect social, vocational, and behavioral adjustment.

1. Introduction

Adolescence is a period of heightened stress (Spear, 2000) due to a confluence of social, academic, cognitive, physiological, and physical changes and demands, marked by physical maturation, drive for independence, increased importance of social and peer relationships, and academic challenges. Given the well-known myriad effects of stress on health (Schneiderman et al., 2005; Ystgaard et al., 1999), understanding how adolescents respond to stress and adversity may provide critical knowledge about the linkage between stress and health, with implications for preventive interventions. Responses to stress are considered a self-regulatory process (Compas et al., 2001; Eisenberg et al., 1997), comprising effortful, volitional coping strategies as well as involuntary, automatic physiological, cognitive, behavioral and affective reactions to stress (Connor-Smith et al., 2000). The degree to which adolescents are able to regulate their emotions, behaviors, thoughts, and physiological responses to stress may function as a mediator and/or moderator of the impact of stress on current and future adjustment and psychopathology, explaining individual differences in the effects of stress (Compas et al., 2001; McLaughlin and Hatzenbuehler, 2009; Sontag et al., 2008).

Although responses to stress and coping could be classified in various ways, a primary dimension is between engagement with vs. disengagement from the stressor, reflecting the "fight or flight" response to threat (Compas et al., 2001). This classification yields engagement coping, disengagement coping (e.g., denial, avoidance), involuntary engagement (e.g., intrusive thoughts, physiological arousal), and involuntary disengagement (e.g., emotional numbing, inaction), although multiple stress responses could be utilized simultaneously and/or successively. Engagement coping can be further divided into primary control strategies involving attempts to control the stressor or emotions related to the stressor (e.g., problem solving, seeking social support) and secondary control strategies involving efforts to adapt to the stressor (e.g., cognitive reconstruction, acceptance) (Compas et al.,

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http://dx.doi.org/10.1016/j.drugalcdep.2017.03.028
Received 21 December 2016; Received in revised form 13 March 2017; Accepted 14 March 2017
Available online 26 May 2017
0376-8716/

2001; Connor-Smith et al., 2000). Studies indicate that both primary and secondary engagement coping tend to be associated with better psychological adjustment (Compas et al., 2001; Sontag et al., 2008), while disengagement (Compas et al., 2001; Min et al., 2007) and involuntary engagement and disengagement (Troop-Gordon et al., 2015; Sontag et al., 2008) are related to poorer adjustment (e.g., more depressive symptoms, aggression, substance use).

Accumulating evidence suggests that prenatal cocaine exposure (PCE) alters responses to stress in reaction to environmental insults (Lester and Padbury, 2009) by disrupting the monoamine neurotransmitter systems important for directing fetal brain development (Kosofsky et al., 1994; McCarthy et al., 2014), particularly in brain areas known to impact emotional and behavioral arousal and regulation and stress response (McCarthy et al., 2014). Studies from multiple longitudinal prospective birth cohorts collectively indicate that PCE is related to greater externalizing behavior problems. PCE effects have been found on teacher- and caregiver-rated externalizing behavior problems at age 7, 9, 11, and 13 years (Bada et al., 2011) and on adolescent-reported externalizing behavior at 12 (Min et al., 2014a) and 15 years of age (Min et al., 2014a,b), with greater effects related to heavier (> 70th percentile) exposure (Min et al., 2014a). Further, PCE is also related to early onset of substance use (Delaney-Black et al., 2011; Frank et al., 2011; Minnes et al., 2014; Richardson et al., 2013) and risky sexual behavior (De Genna et al., 2014; Lambert et al., 2013; Min et al., 2015, 2016), all of which collectively suggest PCE-related altered responses to stress. However, no study has specifically examined response to stress and coping abilities in PCE adolescents to date.

Children with PCE tend to grow up in suboptimal parenting and caregiving environments, characterized by lower levels of maternal education (Singer et al., 2002, 2004), ongoing caregiver substance use and psychological distress (Singer et al., 1997; Minnes et al., 2008; Molnar et al., 2014), and lack of social support (Min et al., 2013a; Nordstrom et al., 2005), conducive to potential child maltreatment. The deleterious effects of childhood maltreatment (CM) have been widely recognized (Teicher and Samson, 2016; De Bellis, 2001), with both retrospective and prospective studies reporting associations between CM and poorer psychological (Buckingham and Daniolos, 2013; Keyes et al., 2011; Min et al., 2007) and physical functioning in adulthood (Felitti et al., 1998; Min et al., 2013b). CM may adversely affect the volume and functionality of brain structures, including the reduction of the hippocampus and corpus callosum, and alter neuroendocrinological mechanisms involved in mediating the stress response such as the hypothalamic-pituitary-adrenal axis (Nemeroff, 2004). However, few studies have examined how CM may interact with PCE to affect stress response and coping abilities in adolescence.

According to the diathesis-stress model, those with a biological vulnerability are disproportionately likely to be affected adversely by an environmental stressor/adversity (Zahn-Waxler et al., 2008). The effects of environmental stressors such as CM are greater among those with a biological vulnerability, as stressors activate the vulnerability. Thus, adolescents with PCE may experience worse outcomes than non-cocaine exposed (NCE) adolescents when exposed to environmental stress such as CM. The current study assessed differences in self-reported involuntary responses to stress and effortful coping in adolescents with and without PCE and explored whether CM moderates the effects of PCE on stress response. Multiple biological and environmental confounders of PCE were assessed and controlled to isolate the effects of PCE and CM, including prenatal exposure to other substances such as alcohol (Larkby et al., 2011), tobacco (Maughan et al., 2004), and marijuana (Goldschmidt et al., 2000), elevated lead (≥10 μg/dL) levels (Lane et al., 2008; Min et al., 2009; Singer et al., 2008), ongoing caregiver postpartum substance abuse (Elkington et al., 2011) and psychological distress (Minnes et al., 2010), poor quality of the home environment (Singer et al., 2008; Min et al., 2014b), and violence exposure (Kobulsky et al., 2016; Frank et al., 2011). Further, lack of ecological resources and support from family, school, and the neighborhood/community which tend to confound with CM (Sippel et al., 2015), were also controlled. We hypothesized that adolescents with PCE would be more reactive to stress (more involuntary engagement and disengagement) and utilize coping strategies less effectively (less primary and secondary control and more disengagement) than adolescents without PCE. Adolescents with PCE who experienced CM were further hypothesized to have poorer stress responses than non-cocaine exposed (NCE) adolescents or maltreated NCE adolescents.

2. Methods

2.1. Sample and procedure

This study included 363 (184 PCE, 179 NCE) adolescents and their birth mothers or caregivers recruited at birth (September 1994–June 1996) from an urban county hospital for a longitudinal investigation of the effects of PCE. All recruited mothers were identified from a high-risk population screened for drug use. Urine drug toxicology screens were performed by the hospital on women who received no prenatal care, seemed to be intoxicated or taking drugs, had a history of involvement with the Department of Human Services in previous pregnancies due to drug use, self-admitted drug use, or appeared to be at high risk for drug use after an interview with hospital staff. Women with a psychiatric history, low intellectual functioning indicated in medical chart review, HIV-positive status, or chronic medical illness were excluded, as were infants with Down syndrome, fetal alcohol syndrome, or congenital heart defects. A nurse recruiter approached 647 screened women immediately before or after infant birth; of these 647 women, 54 were excluded, 155 refused to participate, and 23 did not come to the enrollment visit.

Maternal and infant urine samples and infant meconium were obtained shortly before or after infant birth and analyzed for cocaine and other drug metabolites, including benzoylecgonine, *meta*-hydroxybenzoylecgonine, cocaethylene, cannabinoids, opiates, phencyclidine, amphetamines, and benzodiazepines. A total of 415 newborns and their birth mothers were enrolled at birth, of which 218 infants were identified as PCE based on positive screens of maternal and infant urine, infant meconium, or maternal self-report of cocaine use during pregnancy to hospital or research staff. Infants who were negative on all indicators of PCE were identified as NCE, but they may have been exposed to other substances (i.e., alcohol, tobacco, marijuana), forming a comparison group. Subjects and their caregivers were assessed by separate examiners who were blinded to exposure status at follow-up assessments at 6, 12, and 18 months and 2, 4, 6, 9–12, 15, and 17 years postpartum.

Since birth, 12 (9 PCE, 3 NCE) enrolled children died from sudden infant death syndrome (4 PCE, 2 NCE), cardiopulmonary arrest (1 PCE), pneumonia (1 PCE), accidental asphyxia (1 PCE), respiratory distress syndrome (1 PCE, 1 NCE), and unknown illness (1 PCE). The present study utilizes data from 363 adolescents who completed stress response assessment at age 15 and/or 17 years, representing 90% retention of the 403 living participants in the original study. Among the 363 participating adolescents, 92% (n = 335) were assessed at both 15 and 17 years of age. Of the 40 adolescents not included in this analysis (19 drop-out, 18 lost contact, 2 low intellectual functioning (IQ < 50), 1 missing data), the 25 PCE adolescents did not differ from the 184 participating PCE adolescents. The 15 NCE adolescents not included in the study were more likely to be white, have birth mothers who were older, more likely to be married, and had more years of education compared to the 179 participating NCE adolescents. Fig. 1 charts the flow of participants through the study. The Institutional Review Board of the participating hospital approved this study. All participants were given a monetary stipend, lunch, and transportation costs if needed. Parental written informed consent was obtained, with child assent beginning at age 9. A Certificate of Confidentiality (DA-09-146) was obtained from U.S. Department of Health and Human Services to protect

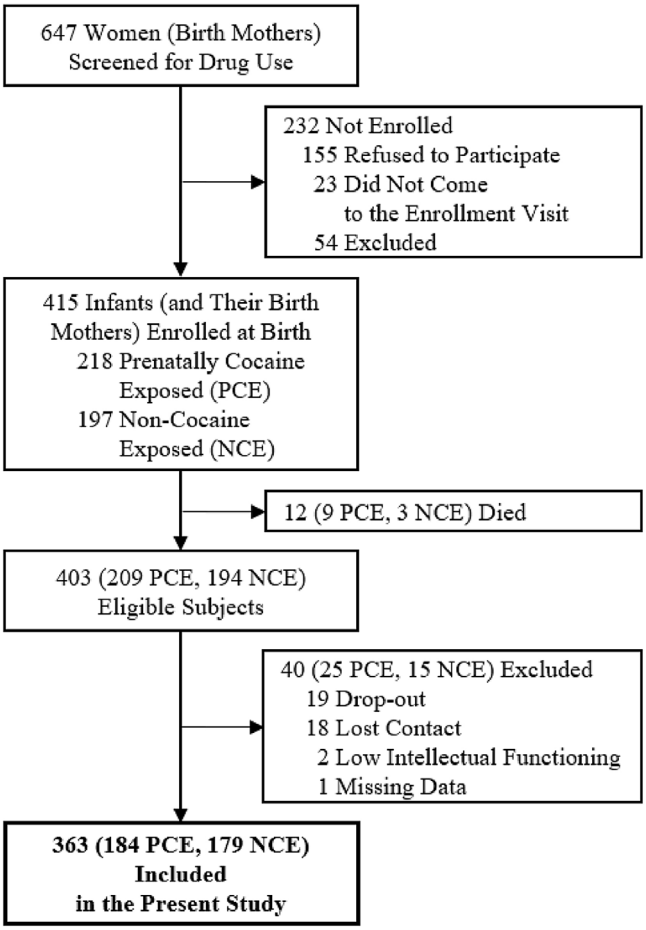

Fig. 1. Participant flow diagram of the study sample.

the release of drug-related information from forced disclosure.

2.2. Measures

2.2.1. Prenatal cocaine and other substance exposures

Birth mothers were asked to recall frequency and amount of drug use for the month prior to and for each trimester of pregnancy at the newborn visit. The number of tobacco cigarettes and marijuana joints smoked per day, and the number of drinks of beer, wine, or hard liquor per week was computed, with each drink equivalent to 0.5 oz. of absolute alcohol. As the majority of women (97%) in our study used the crack cocaine form, the number of "rocks" consumed and the amount of money spent on cocaine per day were noted, and was converted to a standard "unit" of cocaine, referring to $20 worth of crack cocaine. Frequency of use was recorded for each drug on a Likert-type scale ranging from 0 (not at all) to 7 (daily use) 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 score for the month prior to pregnancy and for each trimester. These scores were then averaged to obtain a total average score. The drug assessment was updated with the child's current caregiver at each follow-up visit to assess recent (prior 30-day period) postpartum, caregiver drug use.

2.2.2. Response to stress

Adolescents' responses to interpersonal stress were assessed at ages 15 and 17 years using the Response to Stress Questionnaire (RSQ), a 57-item adolescent self-report (Connor-Smith et al., 2000). The RSQ includes five subscales that tap into both volitional coping strategies (primary control, secondary control, disengagement) and involuntary responses (involuntary engagement, involuntary disengagement). Primary control (α = .79 at 15 years, .77 at 17 years) consists of problem solving and emotional regulation and expression; Secondary control (α = .77, .75) consists of distraction, positive thinking, cognitive restructuring, and acceptance; and Disengagement (α = .77, .81) consists of avoidance, denial, and wishful thinking. Involuntary engagement (α = .89, .90) includes rumination, intrusive thoughts, emotional arousal, physiologic arousal and impulsive action; Involuntary disengagement (α = .85 at both assessments) includes cognitive interference, involuntary avoidance, inaction, and emotional numbing. Items were rated on a 4-point Likert scale indicating the degree to which or frequency with which each response was enacted by the participant (from *not at all* = 1 to *a lot* = 4) in response to interpersonal stress. Scores reflecting the proportion (%) of total responses (i.e., subscale score divided by the total score on the RSQ*100) were used in analyses to control for individual differences in overall responding bias as recommended (Connor-Smith et al., 2000; Vitaliano et al., 1987). Higher scores on a subscale represent a more dominant strategy in adolescent's response to stress.

2.2.3. Childhood maltreatment

At age 17 years, CM was assessed (1 = yes; 0 = no) retrospectively using the Juvenile Victimization Questionnaire (JVQ)-Adult Retrospective Version, a 34-item self-report of childhood victimization (Hamby et al., 2004; Finkelhor et al., 2005). Respondents report the number of times they experienced maltreatment from the time they were born until 17 years of age on a 6-point scale (*None, 1 time, 2 times, 3 times, 4 times, or ≥5 times*), including physical abuse by caregiver, psychological/emotional abuse, neglect, and custodial interference/family abduction. Respondents reporting any incidence of maltreatment to at least one of the four questions on maltreatment were coded 1 (yes).

2.2.4. Confounders

Birth, demographic, and medical characteristics (e.g., maternal age and marital status at birth, years of education of the biological mother, child's race and gender, infant head circumference, etc.) were extracted from hospital birth records. Socioeconomic status was computed using the Hollingshead Two Factor Index of Social Position (Hollingshead, 1957), with a Hollingshead score of IV or V used as an indicator of low socioeconomic status. At the newborn visit, maternal receptive vocabulary was assessed using the Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn and Dunn, 1981) and was updated using the PPVT-III (Dunn et al., 1997) at age 6 and later assessments. Maternal/caregiver self-reported psychological distress was assessed using the Global Severity Index (α = .95), a summary scale of the Brief Symptom Inventory (BSI; Derogatis, 1992) at birth and each follow-up visit. The child's placement (with either biological mother/relative or adoptive/foster caregiver) was also noted at each visit, with updated assessment of the current caregiver's psychological distress if there had been a change in caregiver. Blood lead (μg/dL) was assessed for a subset of children at ages 2 and 4 years. Venous blood samples could not be obtained from some children due to lack of parental consent, excessive stress related to having blood drawn, child sickness or logistical difficulties. Valid hematologic measures were available for 143 two-year and 274 four-year old children. If blood lead was measured at both assessments, measures were averaged (n = 122). A greater percentage of African-American and married women and a lower percentage of foster parents consented to toddler blood collection. Adolescents' intelligence was assessed at age 15 using the Wechsler Intelligence Scales for Children-4th Edition (Wechsler, 2003).

The quality of the caregiving environment was assessed at the 12-year visit using the Home Observation for Measurement of the Environment-Early Adolescent version (EA-HOME; α = .83; Caldwell and Bradley, 2003). Violence exposure was also assessed at the 12 year visit via The Assessment of Liability and Exposure to Substance Use and

Table 1
Maternal and caregiver characteristics.

	PCE (n = 184)		NCE (n = 179)		p
	M	*SD*	*M*	*SD*	
Biologicalmother					
Mother's age at birth	29.75	5.02	25.45	4.72	< .001
Education, years	11.57	1.67	11.92	1.38	.03
Completion of high school, *n* (%)	88	(47.83)	59	(32.96)	.004
Married, *n* (%)	14	(7.61)	28	(15.64)	.02
Parity	3.57	1.89	2.76	1.86	< .001
Number of prenatal visits	5.22	4.59	8.71	4.83	< .001
PPVT-R Standard Score	73.66	14.29	77.70	14.79	.01
BSI Global Severity Index	0.81	0.74	0.51	0.54	< .001
Low SES, *n* (%)	179	(97.81)	175	(97.77)	.97
African-American, *n* (%)	151	(82.07)	146	(81.56)	.90
Substance use during pregnancy	*n* (%)	*M* (*SD*)	*n* (%)	*M* (*SD*)	*p*[a]
Tobacco, cigarettes per day	156 (84.78)	13.30 (10.89)	69 (38.55)	9.55 (8.48)	< .001
Alcohol, drinks per week	144 (78.26)	12.14 (18.98)	72 (40.22)	3.28 (6.72)	< .001
Marijuana, joints per week	77 (41.84)	3.16 (4.78)	16 (8.93)	6.54 (10.06)	< .001
Cocaine, units per week	184 (100)	22.62 (38.15)	–	–	–
Caregiver at age 15	*M*	*SD*	*M*	*SD*	*p*
Education, years	12.53	2.29	12.87	1.95	.13
PPVT-III Standard Score	80.23	14.74	78.72	15.08	.36
BSI Global Severity Index	0.34	0.41	0.34	47	.97
HOME environment	47.87	6.69	48.62	6.17	.27
Substance use, past 30 days[b]					
Tobacco, cigarettes per day	4.82	7.22	3.46	6.57	.01
Alcohol, dose per week	1.56	3.05	2.01	4.67	.33
Marijuana, dose per week	0.54	5.51	0.46	3.10	.62

BSI = Brief Symptom Inventory; HOME = Home Observation for Measurement of the Environment-Early Adolescent version; M = mean; NCE = non prenatally cocaine exposed; PCE = prenatally cocaine exposed; PPVT = Peabody Picture Vocabulary Test, PPVT-R (Revised) was used at birth and PPVT-III (Third edition) was used at 6 and later years; SD = standard deviation; SES = socioeconomic status; WAIS-R = Wechsler Adult Intelligence Scale-Revised.

[a] p-value based on *n* (%).

[b] No caregivers reported cocaine use in the past 30 days.

Antisocial Behavior (ALEXSA; Ridenour et al., 2009), an illustration-based, audio, computer-assisted self-report of antisocial behavior, substance involvement and associated risk factors for children ages 9–12. The ALEXSA violence exposure subscale is composed of 8 items using a 5-point Likert scale (α = .76), assessing lifetime exposure to violence (e.g., beating, robbery, stabbing, shooting), either as a direct victim or witness, with higher scores indicating greater exposure. Ecological resources and support was assessed at age 15 using the External Assets subscale (α = .90) of the widely used Developmental Assets Profile (Search Institute, 2005; Scales and Leffert, 2004), a 58-item youth self-report using a 4-point Likert scale (0 = *not at all or rarely*, 1 = *somewhat or sometimes,* 2 = *very or often*, 3 = *extremely or almost always*). External assets include *Support* (family support and caring school climate and neighborhood), *Empowerment* (community values youth), *Boundaries and Expectations* (clear rules and consequences from family and school), and *Constructive Use of Time* (creative activities and youth programs), with a possible range of 0–30. Higher scores indicate greater assets, with scores < 15 indicating challenged; 15–20 vulnerable; 21–25 adequate; and > 25 indicating thriving assets.

2.3. Statistical analyses

The effects of PCE on stress response were evaluated using a mixed model repeated measures analysis with maximum likelihood estimation procedures. Unstructured covariance matrix was used to account for correlated responses within a subject. The homogeneity of PCE effects over time, as well as the effects of gender and other covariates, on adolescents' stress response was tested by including an interaction term with time. If the interaction was not significant at $p < .10$, the interaction terms were removed from the model. Missing data were modeled using full-information maximum likelihood, which utilizes all available information from the observed data. In order to avoid multicollinearity and saturation of the model, covariates correlated with outcomes at $p \leq .20$ for at least one time point were entered into the longitudinal regression model stepwise and were retained if, on entry, they were significant at $p < .10$ or caused substantial (> 10%) change in the PCE coefficient (Mickey and Greenland, 1989). PCE was entered first followed by socio-demographic covariates, other prenatal substance exposures, caregiving environment, external assets, violence exposure, and maltreatment variables. Due to the reduced sample size, blood lead level was entered last. CM was tested for interaction with PCE. The total stress response was also entered into the model to control for individuals' overall level of stress response proclivity. Adjusted least squares mean (M_{adj}) and standard errors (*SE*) were calculated from the estimated models.

3. Results

3.1. Sample characteristics

Table 1 presents characteristics of birth mothers and caregivers at age 15. The birth mothers of adolescents with PCE were older, less educated, primarily unmarried, had more children and less prenatal care than birth mothers of NCE adolescents. They had lower receptive vocabulary scores and reported more psychological distress and greater use of tobacco, alcohol and marijuana during pregnancy than birth mothers of NCE adolescents. While more than half of the cocaine-using mothers used cocaine throughout pregnancy, the number of mothers using cocaine and the amount of use were gradually decreased over the course of pregnancy: 83% (n = 153) of cocaine-using mothers reporting 36 (*SD* = 62) units of crack cocaine per week in the month prior to pregnancy on average, compared to 73% (n = 135) of cocaine-using mothers reporting 16 (*SD* = 31) units of crack cocaine per week in the third trimester. Also, fewer mothers used tobacco, alcohol, or marijuana as their pregnancy progressed, with less amount of use in both groups. No difference was found in caregiver characteristics at age

Table 2
Adolescent characteristics.

	PCE (n = 184)		NCE (n = 179)		p
	M	*SD*	*M*	*SD*	
At birth					
Gestational age, weeks	37.80	2.78	38.47	2.88	.02
Hobel Neonatal Risk score	7.31	15.74	5.88	15.95	.39
Birth weight, g[a]	2710.1	644.8	3103.6	702.5	< .001
Birth length, cm[a]	47.24	3.87	49.14	3.80	< .001
Head circumference, cm[a]	32.31	2.12	33.47	2.40	< .001
Male, *n* (%)	82	(44.57)	87	(48.60)	.44
African-American, *n* (%)	150	(81.52)	145	(81.01)	.90
Postnatal					
Blood lead level at 2 or/and 4 year[b]	7.07	4.14	8.04	4.66	.06
Elevated lead level (≥10 μg/dL), *n (%)*	26	(17.93)	37	(26.62)	.08
Violence exposure	0.62	0.74	0.57	0.79	.57
Receiving free lunch at school, *n (%)*	147	(83.52)	143	(84.62)	.78
WISC-IV Full Scale IQ at age 15	81.82	10.95	83.80	14.01	.14
Always in birth parents' care by age 15, *n* (%)	55	(30.39)	130	(74.29)	< .001
Adopted/Foster care at age 15, *n* (%)	48	(26.52)	7	(4.00)	< .001
DAP External assets	18.30	4.81	18.75	4.13	.34
Child maltreatment, *n (%)*	53	(30.99)	31	(18.02)	.005
Physical abuse	22	(12.87)	11	(6.40)	.04
Emotional abuse	41	(23.98)	22	(12.79)	.008
Neglect	12	(7.02)	5	(2.91)	.08
Custodial interferences/family abduction	15	(8.77)	11	(6.40)	.41

DAP = Developmental Assets Profile; M = mean; NCE = non prenatally cocaine exposed; PCE = prenatally cocaine exposed; SD = standard deviation; WISC-IV = Wechsler Intelligence Scales for Children-Fourth Edition.
[a] Adjusted for gestational age.
[b] Sub-sample of 145 PCE and 139 NCE.

15, except that caregivers of the adolescents with PCE smoked more cigarettes in the past 30 days than the caregivers of NCE adolescents. Adolescent characteristics are presented in Table 2. Adolescents with PCE had a shorter gestational age, lower birth weight, length, and head circumference, were less likely to be continuously cared for by their birth parents, and reported more physical and emotional abuse than the NCE adolescents. No group differences were found in violence exposure or external assets, with both groups' external assets scores falling in the vulnerable (≤ 20) range.

Table 3 indicates that adolescents with PCE utilized primary control less dominantly at age 15 but disengagement more dominantly at both 15 and 17 year assessments, compared to NCE adolescents. No difference was found in overall stress response proclivity between the groups. Regardless of PCE status and assessment ages, secondary control involving efforts to fit with the environment (acceptance, cognitive restructuring) was the most dominantly used response to interpersonal stress (~26%), followed by involuntary engagement, primary control, and involuntary disengagement. Disengagement (~15%) was the least dominantly used stress response. Bivariate correlations between key variables are presented in Table 4 by PCE status.

3.2. Associations of PCE and childhood maltreatment with response to stress

Table 5 summarizes the associations of PCE and CM with stress responses reported at 15 and 17 years after controlling for covariates and the overall levels of individual stress responses. Significant interactions between PCE and CM were noted on all RSQ subscales except involuntary disengagement (Fig. 2). Adolescents with PCE and CM used primary control (17.36%) less dominantly than adolescent with PCE without CM (18.97%), NCE adolescents with CM (18.83%), and NCE adolescents without CM (18.81%), all p's < .03, at both the 15- and 17-year assessments. Adolescents with PCE and CM also reported less dominant use of secondary control (25.31%) than adolescents with PCE without CM (26.86%) and NCE adolescents without CM (26.32%), all p's < .036. Adolescents with PCE and CM reported more dominant use of disengagement (16.06%) than others at both assessments: adolescents with PCE without CM (15.11%), NCE adolescents with CM (14.81%), or NCE adolescents without CM (14.95%), all p's ≤ .005. Adolescents with PCE and CM also reported more dominant reaction to stress with involuntary disengagement (17.90%) than PCE adolescents without CM (17.02%), p = .02. No PCE or PCE by CM effects were found on involuntary engagement, although CM was related to increased involuntary engagement. Higher levels of endorsement of stress responses were related to less dominant use of primary and secondary control, yet more dominant use of disengagement, involuntary engagement, and involuntary disengagement.

3.3. Other prenatal exposures and environmental factors associated with responses to stress

African American adolescents used more disengagement. Prenatal marijuana exposure was related to more involuntary disengagement. Better home environment was related to more primary control, less disengagement and less involuntary disengagement. External assets were related to all voluntary coping strategies and involuntary responses to stress, such that higher external assets were related to more primary and secondary control, less disengagement, and less involuntary engagement and disengagement. Violence exposure assessed at age 12 was related to less dominant use of secondary control and more dominant reaction to stress with involuntary disengagement. Preschool blood lead level was not related to stress responses (all p's > .19).

Table 3
Responses to stress by prenatal cocaine exposure status and age.

	15 year			17 year		
	PCE (n = 181)	NCE (n = 175)	p	PCE (n = 171)	NCE (n = 171)	p
Test age, *M (SD)*	15.69 (0.27)	15.67 (0.27)	.47	17.82 (0.26)	17.80 (0.25)	.48
Responses to Stress, *M (SD)*[a]						
Primary control	18.38 (3.90)	19.26 (3.92)	.03	17.94 (3.61)	18.59 (3.57)	.10
Secondary control	26.35 (4.18)	26.45 (4.32)	.84	25.70 (4.40)	25.31 (4.32)	.20
Disengagement	15.42 (2.25)	14.82 (2.50)	.02	15.61 (2.46)	14.95 (2.37)	.01
Involuntary engagement	22.32 (3.70)	22.23 (3.55)	.80	22.93 (4.00)	22.83 (3.65)	.80
Involuntary disengagement	17.52 (3.08)	17.25 (2.92)	.38	17.81 (3.25)	17.32 (2.91)	.14
Total responses to stress	132.62 (26.25)	128.37 (25.41)	.12	140.89 (25.79)	136.69 (26.70)	.14

[a] Responses to stress are reported as the proportion (%) of total responses. M = mean; NCE = non prenatally cocaine exposed; PCE = prenatally cocaine exposed; SD = standard deviation.

Table 4
Correlations between key variables, with PCE below the diagonal (n = 184) and NCE above the diagonal (n = 179).

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Sex, male	–	−.13	.04	−.22	−.14	.12	−.03	−.04	−.002	.02	−.01	.06	−.19
2. African American	−.02	–	−.08	.06	.15	.04	−.15	−.13	−.02	.12	.00	.10	.10
3. Prenatal marijuana exposure	.06	−.11	–	−.02	−.002	−.09	−.07	−.05	−.09	.04	.04	.11	.01
4. HOME score	.01	−.09	.04	–	.22	−.15	−.14	.21	.12	−.21	−.11	−.15	.02
5. External asset	.09	−.11	.11	.25	–	−.22	−.21	.34	.24	−.13	−.32	−.30	−.02
6. Violence exposure	.12	.22	−.05	−.17	.05	–	.23	−.14	−.21	.01	.28	.15	.08
7. Childhood maltreatment	−.04	.01	.13	.03	−.003	.16	–	−.17	−.21	.05	.29	.14	.29
Responses to Stress at age 15													
8. Primary control	.07	−.05	−.01	.22	.32	−.19	−.18	–	.35	−.60	−.56	−.66	−.36
9. Secondary control	.16	−.08	.005	.09	.21	−.18	−.26	.38	–	−.35	−.81	−.65	−.46
10. Disengagement	−.12	.12	−.10	−.12	−.18	.15	.23	−.52	−.32	–	.21	.21	.24
11. Involuntary engagement	−.08	−.01	.01	−.12	−.25	.14	.19	−.65	−.74	.15	–	.55	.47
12. Involuntary disengagement	−.13	.10	.07	−.17	−.26	.20	.17	−.62	−.71	.19	.51	–	.39
13. Total responses to stress	−.20	.10	.04	−.01	−.06	.07	.22	−.35	−.53	.20	.49	.43	–

Note. $p < .05$ when r ≥ |.15|; $p < .01$ when r ≥ |.20|; $p < .001$ when r ≥ |.25|.

Table 5
Effects of prenatal cocaine exposure and childhood maltreatment on responses to stress at ages 15 and 17 years.

	Primary Control			Secondary Control			Disengagement			Involuntary Engagement			Involuntary Disengagement		
	b	*SE*	*p*	b	*SE*	*p*	b	*SE*	*p*	b	*SE*	*p*	b	*SE*	*p*
PCE	.17	.35	.63	.55	.36	.13	.17	.24	.49	−.38	.28	.18	−.47	.28	.10
Age, 17 year	−.23	.21	.26	.21	.22	.36	.03	.14	.85	.14	.20	.49	−.12	.17	.50
Sex, male	−.11	.32	.73	.60	.32	.06	−.15	.22	.49	− .08	.29	.77	−.30	.25	.24
African American	−.75	.42	.07				.77	.28	.007				.24	.33	.47
Prenatal marijuana exposure													.59	.19	.002
HOME score	.08	.02	.002	.01	.03	.56	−.04	.02	.02	− .02	.02	.46	−.04	.02	.04
External assets	.16	.04	< .001	.18	.04	< .001	−.05	.02	.03	− .17	.03	< .001	−.13	.03	< .001
Violence exposure	−.21	.21	.31	−.54	.21	.01	.10	.14	.47	.34	.19	.07	.41	.17	.01
Childhood maltreatment	.02	.58	.97	−.07	.58	.90	−.13	.40	.74	.89	.34	.01	−.33	.48	.50
PCE*Childhood maltreatment	−1.63	.74	.03	−1.48	.74	.047	1.08	.50	.03				1.21	.60	.047
Total responses to stress	−.05	.006	< .001	− .08	.006	< .001	.02	.004	< .001	.07	.005	< .001	.04	.005	< .001

Note. Blank spaces indicate that the variable did not meet the criteria (e.g., not significant at the bivariate level) and therefore not included in the model. PCE = prenatal cocaine exposure; SE = standard error.

4. Discussion

PCE was associated with poorer coping strategies only among adolescents with a history of CM, even after controlling for other biological and environmental confounders. Adolescents with PCE who experienced CM reported less dominant use of primary (problem solving and emotional regulation) and secondary control (acceptance and cognitive restructuring) and greater use of disengagement (denial, avoidance, and wishful thinking) coping strategies than adolescents with PCE without CM or NCE adolescents regardless of CM. They also reacted to stress with involuntary disengagement (cognitive interference and emotional numbing) more dominantly than NCE adolescents. PCE effects can be exacerbated or ameliorated by the aspects of the environmental context (Vorhees, 1989). PCE-related impaired arousal regulation predisposes children to a lower threshold for activation of “stress circuits” and may increase their vulnerability to the deleterious effects of stressful conditions (Mayes et al., 1998). Our findings indicate that PCE may increase vulnerability to or amplify the effects of CM and yield ineffective stress responses in late adolescence, consistent with two previous studies. Molnar et al. (2014) reported that PCE children high in caregiving environmental risk (combination of maternal psychopathology, exposure to violence, and caregiving instability) had the riskiest trajectory of externalizing behavior problems in early childhood (18–54 month of age). Similarly, another prospective study (Yumoto et al., 2008) reported greater vulnerability to even lower levels of environmental risk (e.g., low socioeconomic status, parental violence, maternal depression, negative life events, current/ongoing substance use) in children with prenatal alcohol or cocaine exposure, compared to non-exposed children, indicated by lower IQ and higher teacher-reported delinquent behavior and internalizing problems at age 7. Despite methodological differences in operationalization of environmental stressors, outcome variables, and assessment ages, these studies, along with the present study, are consistent with a model of biological vulnerability to heightened stress reactivity as a function of PCE.

The present study indicated that more adolescents with PCE were maltreated than NCE adolescents, which could lead to an alternative interpretation of the finding: rather than CM moderating the effect of PCE, CM may mediate the effects of PCE on stress response. When a predictor variable and a moderator are correlated, a statistical interaction between the two variables in predicting an outcome could indicate mediation rather than moderation (Kraemer et al., 2008). However, given that mediation implies causation, it is unlikely that PCE causes CM. It is more plausible that PCE is a marker of overall life adversity including the lack of adequate parenting and caregiving, subject to CM (Belsky, 1993). Future studies examining the role of life adversity including CM in the context of PCE will enrich our understanding of PCE effects on the transactional developmental pathways of behavioral adjustment.

Independent of PCE, CM, and other biological risk factors, violence exposure was additively related to less dominant use of secondary control and more dominant reaction to stress with involuntary disengagement, underscoring the significance of adverse events in shaping one’s stress responses. Continued, multiple exposures to stress overburdens adolescents’ coping resources, reducing the ability to respond effectively to stressful situations, which may increase the risk of psychopathology (Grant et al., 2003). Greater external assets, reflecting supportive relationships and opportunities offered by family, school, and community/neighborhood, were related to more effective stress

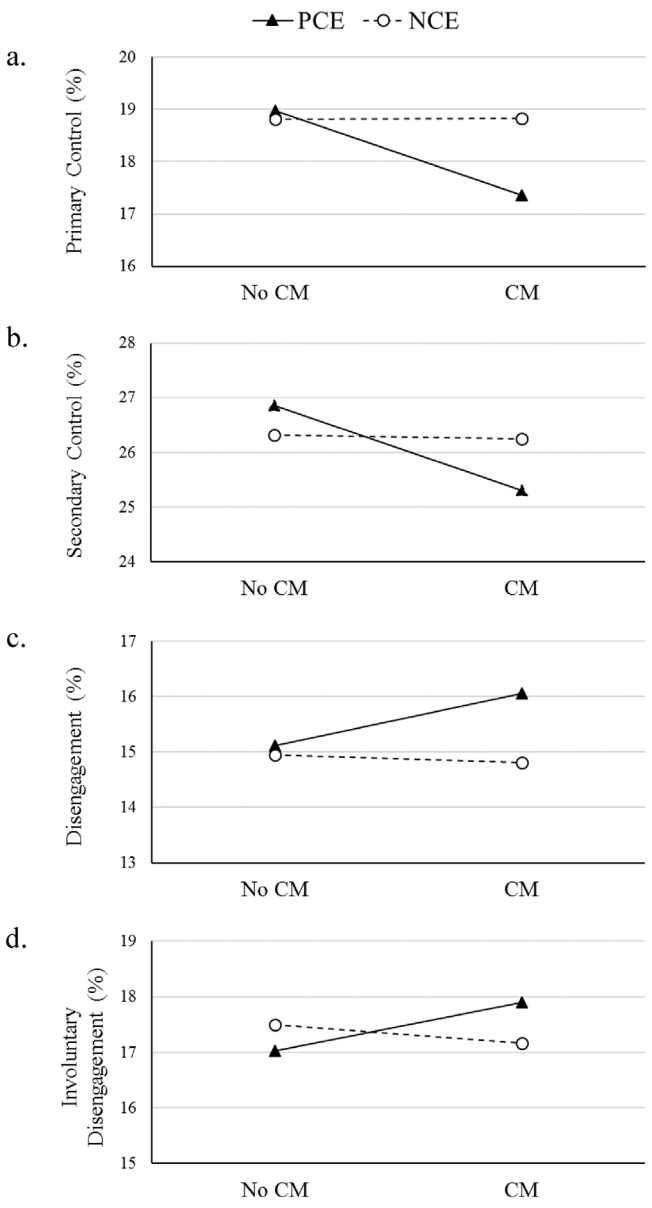

Fig. 2. Response to stress using a) Primary Control, b) Secondary Control, c) Disengagement, and d) Involuntary Disengagement by prenatal cocaine exposure (PCE) status and childhood maltreatment (CM) adjusted for covariates listed in Table 5.

responses (more dominant use of problem solving and emotional regulation and less engagement in denial and wishful thinking). Given that the overall level of external assets was in the vulnerable range in this sample, our findings suggest that interventions and policies supporting the improvement of external assets might be promising in promoting more optimal stress responses, possibly by compensating for the effects of PCE and CM, and thus increasing resiliency even in high-risk adolescents afflicted by PCE and CM.

Several limitations in our study must be acknowledged. Although biological measures were used for detection of PCE, prenatal drug assessment was obtained retrospectively and thus subject to recall error and social desirability bias. Similarly, the validity of an adolescent retrospective self-report measure of CM may be compromised by fallibility of memory. Although retrospective reports are sufficiently valid to be used for research purposes and under-reporting is more common than over-reporting (Hardt and Rutter, 2004), lack of explicit details of the CM (duration, age at which maltreatment first occurred, relationship to perpetrator) might not fully account for the experience of CM and its relationship with stress response. The sample composition limits generalizability of the findings to low-income, urban, predominantly African-American adolescents whose mothers lacked prenatal care and/or exhibited signs of intoxication at delivery. Finally, our observational design cannot rule out that the apparent effects of PCE on stress responses could be attributable to unmeasured genetic factors (D'Onofrio et al., 2013) and other biological and environmental confounders of PCE.

The present study has multiple strengths. The longitudinal prospective design, assessment of a large number of adolescents and caregivers since birth with 90% retention in late adolescence, careful measurements with biologic and maternal report of prenatal drug exposure, and assessment of a large number of confounding variables, including blood lead levels, maternal psychological distress, violence exposure, and external assets available to adolescents, enhance confidence in the findings.

In conclusion, CM moderated the effects of PCE on stress responses. Adolescents with PCE who experienced CM used poor and inadequate stress responses and coping strategies, supporting PCE as a diathesis. Interventions and policies supporting the improvement of external assets may promote better stress responses and thus increase resiliency even in high-risk adolescents afflicted by PCE and CM. Continued studies into adulthood will elucidate how coping and involuntary stress responses affect social, vocational, and behavioral adjustment.

Contributors

Dr. Meeyoung O. Min conceptualized the paper, performed the statistical analyses, and wrote the initial and final draft. Dr. Sonia Minnes designed the study and interpreted the data. Ms. June-Yung Kim assisted in the literature review, drafting, and proofing the manuscript. Ms. Miyoung Yoon assisted in the literature review and drafting the manuscript. Dr. Lynn T. Singer participated in the study's conception and design, interpretation of data, and reviewed the manuscript. All authors read and approved the final manuscript.

Role of funding source

This research was supported by the National Institute on Drug Abuse (NIDA)R01 07957. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Drug Abuse or the National Institutes of Health.

Conflict of interest

No conflict of interest declared.

Acknowledgements

The authors would like to thank all of our families who participated in our research for 17 years. We would also like to thank Adelaide Lang, PhD for reviewing early drafts, and Laurie Ellison, LISW, and Paul Weishampel, MA for research assistance.

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