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Teens With Heavy Prenatal Cocaine Exposure Respond to Experimental Social Provocation with Escape Not Aggression

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Abstract

Preclinical data show that, compared to no exposure, prenatal cocaine exposure (PCE) has age-dependent effects on social interaction and aggression. The aim of this clinical study was to determine how heavy/persistent PCE – after controlling for other prenatal drug exposures, sex and postnatal factors – predicts behavioral sensitivity to provocation (i.e., *reactive aggression*) using a well-validated human laboratory model of aggression. African American teens (mean = 14.2 yrs old) with histories of heavy/persistent PCE (maternal cocaine use ≥ 2 times/week during pregnancy, or positive maternal or infant urine/meconium test at delivery; $n = 86$) or none/some exposure (NON: maternal cocaine use < 2 times/week during pregnancy; $n = 330$) completed the Point Subtraction Aggression Paradigm. In this task, teens competed in a computer game against a fictitious opponent. There were three possible responses: (a) *earn* points, to exchange for money later; or (b) “*aggress*” against the fictitious opponent by subtracting their points; or (c) *escape* temporarily from point subtraction perpetrated by the fictitious opponent. The PCE group responded significantly more frequently on the *escape* option than the NON group, but did not differ in aggressive or money-earning responses. These data indicate that PCE-teens provoked with a social stressor exhibit a behavioral preference for escape (negative reinforcement) more than for aggressive (retaliatory) or appetitive (point- or money-reinforced) responses. These findings are consistent with preclinical data showing that social provocation of adolescent or young adult offspring after PCE is associated with greater escape behavior, inferring greater submission, social withdrawal, or anxiety, as opposed to aggressive behavior.

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Conflicts of interest

The authors do not have any conflicts of interest regarding this work.

Keywords

Prenatal cocaine exposure; Maternal alcohol use; Aggressive behavior; Escape; Social provocation

1. Introduction

At the peak of the 1980's cocaine epidemic, up to 30% of infants born in urban hospitals were prenatally exposed to cocaine [51]. Although the incidence of prenatal cocaine exposure (PCE) has decreased since then [45], information about the long-term behavioral consequences of PCE remains incomplete. Several research teams, including our own, have identified PCE-related central nervous system-mediated deficits in early school-age children, including problems of arousal regulation [26], externalizing behaviors ([4,26,50,58; but see [1]), and internalizing behaviors [4].

Preclinical studies have demonstrated that PCE *versus* no exposure has age-dependent effects on social interaction. Specifically, daily high-dose gestational cocaine exposure increased submissive behavior during play in juvenile male rats [65] and reduced social contact in periadolescent (postnatal day [PND] 30) male and female rats [52], young adult (PND 60–90) male rats [39], and adult (PND 120) male and female rats [52]. However, using a different task in which a triad of animals had to compete for water, adolescent PCE rats exhibited greater aggressive behavior than non-exposed controls [66]. In older adult (PND 180) male/male interactions, PCE significantly increased aggressive behaviors using the “resident intruder” paradigm where an unfamiliar rat, matched on age and sex, is placed in their home cage [38]. While data remain limited, these results suggest that PCE may produce a developmental progression of socially mediated effects that range from anxious/avoidant-type reactions during adolescence to increasingly aggressive reactions during adulthood.

The present clinical study was undertaken as part of an ongoing prospective, longitudinal cohort design to determine how PCE influences behavioral sensitivity to social provocation using a well-validated human laboratory model of aggression [3,11,13,14,¹⁵,16,18,19,20,21,²²,41,42,43,46] in a sample of African American urban teens at about 14 years of age. Aggressive behavior on this laboratory task is correlated with an aggressive behavioral history, including childhood conduct disorder [17,47,48].

2. Materials and Methods

2.1. Participants

Adolescent participants were originally identified through a prospective pregnancy study that recruited women receiving prenatal care at our University maternity hospital in 1989–1991. Research staff extensively screened pregnant women for their use of tobacco, alcohol and illegal drugs – especially cocaine – with a structured interview at each prenatal visit. Inclusion criteria for the longitudinal study were singleton birth between September 1, 1989 and August 31, 1991 ($N = 656$), and continued residence in the Detroit area at the age 7. Among the 656 identified and contacted, 556 (85%) were assessed at the 7-year visit; 432 of these same children were seen at the 14-year follow-up. Exclusion criteria for the longitudinal child study included multiple gestation (e.g., twins or triplets), children born to women known to be HIV positive, and children with multiple congenital malformations. Offspring from repeat pregnancies to the same participating mother were also excluded. A comprehensive set of age-14 year assessments was scheduled. Each participant attended the testing facility, located in an outpatient clinic setting.

2.2. Prenatal Cocaine Exposure (PCE)

Evidence of prenatal cocaine exposure (PCE) was obtained prospectively from laboratory testing and historical sources: 1) prospective structured interviews conducted throughout pregnancy; 2) the prenatal clinic record; 3) hospital records (including mother's self-reported in-pregnancy drug use, obtained at delivery by obstetrical and nursery staff); and 4) retrospective report at the age-7 or age-14 year follow-ups. Objective evidence of PCE consisted of positive maternal urine collected at the prenatal visits or delivery, and positive neonatal urine or meconium (which was initiated toward the end of study recruitment, and hence available for <10% of the sample).

In the present analyses, PCE was modeled *a priori* as a dichotomous measure: "None/Some" versus "Heavy/Persistent", using the following rationale. Based on our previous work [24,25,26], cocaine-related behavioral effects were found in children with either heavy or persistent exposure but not in children with less or no prenatal cocaine exposure. We statistically confirmed no differences between teens with None vs. Some PCE (within the NON group) in the present data set; this issue is not discussed further. Similar findings regarding levels of exposure have also been reported in other alcohol/drug-exposed cohorts [36].

We defined "Heavy/Persistent" PCE as maternal use of cocaine two or more times per week during pregnancy ("Heavy"), or continued cocaine use throughout pregnancy, based on a positive maternal urine sample at or within a week of delivery or a positive neonatal urine or meconium sample ("Persistent"). Infants with a positive biospecimen at delivery or whose mothers had a positive urine sample were considered persistently exposed (i.e., continued cocaine exposure throughout pregnancy). It is assumed that mothers of these children used cocaine consistently until giving birth, as evidenced by positive maternal and/or infant urine testing at delivery. While it is possible that a woman could use cocaine for the first time just days before delivery, given the nature of cocaine dependence and the contemporary social and legal climate, it is unlikely. It seems likely that only those women who use cocaine regularly and are unable to abstain from use, would even be tempted to use cocaine at that point. By default, all other teens without this amount/extent of PCE were categorized in the None/Some group.

2.3. Point Subtraction Aggression Paradigm (PSAP)

The PSAP task is a computer-based game in which each participant competes individually against a fictitious opponent to earn points or avoid losing points, or to subtract points from their opponent (i.e., the aggressive response). The task version used in the present study offered three simultaneously available operant responses (e.g. [14,15,18,46]), which were exercised by pressing one of three buttons repeatedly (i.e., 3 Fixed Ratio [FR] schedules of reinforcement) on a computer console. Parametric research with this task has established that manipulating the response requirements (i.e., FR performances) on one button option can influence the allocation of responding. Not surprisingly, if response requirements to earn points/money are easy (minimal FR value), then subjects are biased to respond for money [41]; likewise, increasing the response requirement to subtract points from the opponent reduces responding on that option [20]. As a result, the response requirement to earn points/money in this procedure has typically been fixed at a 10-fold higher level (FR 100) than the response requirement for each of the two other options (both FR 10). Based on those parametric studies, virtually all experiments have used the task parameters that were adopted for the present study.

The research assistant first instructed the participant on the task, as follows:

“The purpose of the procedure is to determine the relationship between mood and motor responses. You will be working at a response panel, which contains three buttons marked A, B and C – each with a different outcome – and a money counter. You are participating through the console with another person located at another facility. You can earn points that will be exchanged for money. You can earn points, 10 cents at a time, by pressing Button A 100 times. The other person can subtract your points 10 cents at a time, and each point they subtract is added to their counter. You can subtract points (10 cents at a time) from the other person by pressing Button B 10 times. However, any points you subtract from the other person will *not* be added to your total. You can briefly escape from having points subtracted by the other person by pressing Button C 10 times. During the session, you can choose which button to press; however, once you select an option, you must complete the response sequence associated with that option before you can select the next option.”

During this brief instruction period (which was shorter than the actual experimental session), the participant was able to observe and respond. This helped to confirm that the participant comprehended the task. After this explanation, the experimenter answered any questions the subject had about the procedure. Each teen then completed one session of the PSAP task alone while seated in a private testing room.

Thus, subjects could choose Option A; *Fixed ratio (FR) 100* pressing button ‘A’ on the response panel 100 times in a row enabled the participant to earn points that would be exchanged for money at the end of the testing day (@ 10 cents/point); or Option B; *FR 10*: pressing the adjacent button ‘B’ on the console 10 times in a row permitted the subject “to aggress” against, i.e., take points/money away from, the fictitious opponent who was putatively connected to the computer system and simultaneously engaged in the same task; or Option C; *FR 10*: the subject could opt for a variable-interval time-out (i.e., escape) from point subtraction by the fictitious opponent. In reality, points were subtracted from the subject according to a pre-determined schedule using the computer software (see below). Option B responses actually resulted in the subject temporarily escaping from having his/her points subtracted (i.e., similar to Option C); however, the subject was not explicitly informed of this contingency for Option B. In short, the consequences for Option B and Option C were identical, but were associated with different instructions, i.e., aggressive (Option B) *versus* escape behavior (Option C).

The participant could press any button they wanted to initiate a new response option, but once chosen, the full number of responses associated with that alternative (i.e., FR 100 for Option A or FR 10 for Options B or C) had to be pressed before initiating another option. The computer software nonetheless records any additional responses (e.g., button B or C responses that occur while completing the FR 100 requirement for button A); however, these responses do not count toward completion of those options. Inspection of the data found that these additional responses were very infrequent and thus, those data are not discussed further.

Frequency of point subtraction (i.e., the provocation to the subject) determines the rate of Option B responding in this paradigm [13,19,21]: In the absence of point subtractions, very low rates of *unprovoked* aggressive responding are observed [43]. In short, this task measures reactive rather than proactive aggression. Point subtraction has been shown to elicit aggressive responding in children with attention deficit hyperactivity disorder, an effect that was decreased by treatment with methylphenidate [11]. In previous studies, aggressive behavior was maintained only if point loss was attributed to another person (or fictitious opponent) with whom the subject was paired and was reinforced by perceived avoidance of point loss [41]. In the present study, we deliberately selected a more frequent

rate of provocation from the computer task software menu to probe the sensitivity of participants to this social challenge. By adopting this approach, we attempted to bias participants toward a higher rate of aggressive and/or escape (relative to money-maintained) responding so that underlying group effects would be more likely to be revealed.

Importantly, aggressive responding during the three-option procedure is not required because an equally effective – in terms of points earned or points not lost – non-aggressive response (i.e., escape) is concurrently available. Thus, subjects can protect money they have earned without responding aggressively and, in fact, it has been demonstrated that the presence of the escape option significantly reduces but does not eliminate aggressive responding relative to the absence of an escape option [46]. The computer program enables the experimenter to select *a priori*, from several possibilities, the average provocation-free interval (PFI) for the entire task session, although PFIs vary during the session because the subject can choose to delay point subtractions by responding on Option C (and Option B although, as noted above, that is not made explicit in the instructions). In the present study, the PFI was set to be relatively short to maximize the likelihood of eliciting aggressive or escape responses. The participant was not told how long the PFIs lasted.

2.4. Other assessments

Covariates assessed included a modified laboratory version of the *Home Observation for Measurement of the Environment* total score [8], which assesses the home environment and parenting quality; primary (victimization) and secondary (witnessed) community violence exposure that was self-reported at age 7 years based on the *Things I Have Seen and Heard* [54], and self-reported at age 14 years based on the *Survey of Exposure to Community Violence* [55] and the *Children's Report of Exposure to Violence* [23]; the *Child Health and Illness Profile - Adolescent Edition* (CHIP-AE [63]), which measures health risk behaviors including the teen's drug use; maternal and child psychopathology based on DSM-IV criteria using the PDQ-4 [35] and the K-SADS-PL [40]; the *Achenbach Child Behavior Checklist – Teacher Report Form* (CBCL–TRF) internalizing and externalizing scale scores [2]. In addition, analyses controlled for primary caregiver education level, IQ, marital status, 14-year socioeconomic status based on the *Hollingshead Index of Social Position* [33], and other pre- and post-natal alcohol and drug use. Prenatal exposure during pregnancy was obtained via maternal self-report (alcohol, nicotine, opiates, & marijuana) and urine screen (cocaine & opiates). A reliable screening instrument used to detect problem drinking, the Michigan Alcoholism Screening Test (MAST [57]), was also administered. Postnatal drug exposure was based on self-report (alcohol & all drugs) and on biologic hair analysis (cocaine & opiates) at the 14-year follow-up assessment.

2.5. Statistical analyses

Prior to analyses addressing the hypotheses, checks were performed for missing and out-of-range data, and for normality. Initial analyses described PSAP performance on response Options A, B and C, separately for PCE and NON groups, and for each sex. As noted above, numerous postnatal variables were assessed and these were considered in the present analyses. Control variables were selected for inclusion in forward stepwise multiple regression analyses, which were conducted separately for Option A (point/money), Option B (escape) and Option C (escape) responses, based on the strength of their relationships to the outcome. All control variables that were even modestly related to each outcome (at $p < 0.10$) were included as potential control variables in the first block of the stepwise process. Criteria for entry and removal were $p \leq 0.05$ and $p > 0.10$. After inclusion of all control variables, two dummy variables representing prenatal cocaine exposure were entered. The first dummy variable compared persistent exposure versus none and some combined (PCE versus NON). The second dummy variable compared none versus some exposure.

3. Results

3.1. Group classification

At the approximate age 14-year prospective follow-up assessments, 432 teens were tested in the overall battery (see Table 1 for a description of sample characteristics). Participants with complete PSAP data ($n = 416$; 214 males and 218 females) were included in the present univariate analyses; however, sample size was slightly lower for some multivariable analyses as indicated. Within this sample, 86 teens (21%) were classified as having had “heavy/persistent” prenatal cocaine exposure (PCE), as defined above. In contrast, 330 subjects (79%) were classified as having had “none/some” exposure (NON) (see Table 2). Data checks indicated that the variables assessed in this study were normally distributed. The amount of missing data was small, and was not specific to PCE/NON group.

3.2. Univariate analyses

On average (mean $\pm$ 1 SD), there were 16.7 ± 3.2 point subtractions (“provocations”) per session, or about one every 72 sec, and a manipulation check confirmed that the rate of point subtraction did not significantly differ between PCE and NON groups. The PCE group responded 23% more frequently on the ‘escape’ option than the NON group (406 ± 250 vs. 329 ± 223 , respectively), $t(1,414) = 2.69$, $p = 0.007$. However, PCE and NON groups did not differ significantly in overall responding for points/money (3122 ± 773 vs. 3293 ± 911 , respectively), for the ‘aggressive’ option (204 ± 147 vs. 198 ± 169 , respectively), or total A+B+C responding across all three options (PCE: 3730 ± 751 vs. NON: 3807 ± 846). On average, both groups had similar net earnings of about \$4.30 during the 20-min session. Although teens were compensated at a fixed rate for their time and effort in the 8-hour assessment battery (which involved many other assessments, some of which are noted above), the money they obtained for the PSAP task was response-contingent (i.e., there was no increase in base-rate compensation for the 20-min session).

3.3. Multivariable analyses

Hierarchical regression modeling, first entering all covariates (detailed above) in a stepwise manner, including other prenatal exposure variables and sex, and then prenatal cocaine exposure (PCE), was used to assess the relative contributions of these factors to escape responding (Option C). In the final model, PCE and maternal levels of postnatal alcohol drinking at child age 7 years (grouped in Table 2 and Figure 1 as low (< 1 drink/day) *versus* high (≥ 1 drink/day) average consumption) predicted significantly greater escape responding. For total Option C responses (top panel of Figure 1), significant predictors of greater responding were PCE, higher maternal alcohol intake at child age 7, teen female sex, and number of task point subtractions (see Table 3 for predictor coefficients), $F(5,371) = 7.01$, $p < 0.001$; adjusted $R^2 = 0.07$. Although the PCE and NON groups did not significantly differ in the number of task point subtractions, there were still individual differences within each group due to variable frequencies of provocation that led to variation in ‘escape’ response rates. To help refine our interpretation, we therefore conducted a parallel regression to predict the number of Option C responses per subtraction (bottom panel of Figure 1), a measure that controls for the task variable of provocation frequency. In this latter analysis, the significant predictors of greater responding were PCE, higher maternal alcohol use at child age 7, and maternal across-pregnancy alcohol intake (see Table 3); $F(5,370) = 6.30$, $p < 0.001$; adjusted $R^2 = 0.07$).

We examined how higher levels of maternal alcohol use at child age 7 years might have contributed to greater escape responding (Option C). Hierarchical regression analyses was used to examine the influence of maternal post-partum history of psychopathology (measured with the PDQ-4) evaluated at the 14 yr follow-up visit, or the child’s anxiety or

depression symptoms (measured with the K-SADS-PL), perhaps in response to maternal drinking, influenced these findings. However, these measures were not significantly associated with PSAP performance.

In a separate hierarchical regression model, conduct disorder/oppositional defiant disorder symptoms, but not PCE, modestly but significantly predicted greater aggressive responding (standardized $\beta = 0.10$, $p = 0.04$, adjusted $r^2 = 0.01$). The PCE and NON groups did not significantly differ in their rates of conduct disorder, oppositional disorder or maternal alcohol use. However, we observed a significant correlation between the caregiver MAST total score and teen CBCL-TRF internalizing score ($r = 0.12$, $p = 0.013$).

4. Discussion

Few prospective longitudinal clinical research studies have yet determined whether PCE alters key problem behaviors into the teenage years. Preclinical studies have demonstrated that PCE has age-dependent effects on responses to social-interactive and physical-stress challenges. Some of these studies have found that PCE increases aggression [38,66], whereas other studies demonstrated that PCE leads to motivationally opposite (avoidant) behaviors such as social withdrawal [39,52] or submissive behavior [65]. The present clinical study used a well-validated human laboratory procedure that relies on a perceived socially mediated challenge or attack – i.e., provocation (point/money subtraction from their earnings), which is attributed to another albeit fictitious study participant – to stimulate responding. In this paradigm, adolescent subjects had three options with which they could respond freely: work to earn points, aggress against their fictitious opponents (by subtracting points from them), or escape temporarily from having points subtracted.

The primary finding of this study is that PCE significantly increased escape responding but not aggressive responding to experimental social provocation. This outcome is consistent with preclinical data in periadolescent rats [52,65], whose ages correspond to the early teen sample that was tested in this study. These results were independent of prenatal tobacco and alcohol exposures and numerous postnatal environmental factors that were included as covariates in the statistical model. This finding increases confidence that increased escape responses in young teens are specific to prenatal cocaine, as opposed to other prenatal drug exposures, and that a number of salient postnatal environmental factors do not account for this behavioral response to social provocation for these teens.

Another significant finding was that higher self-reported levels of maternal postnatal alcohol consumption at child age 7 years independently predicted greater escape responding from provocation. It is possible that the multiple social stressors encountered by caregivers and teens from this urban population sample – including low levels of SES, education and income, and high levels of substance use and community violence – could occasion alcohol use. This coping behavior might, in turn, function as a model of escape or internalizing behavior for the child. Under these assumptions, the impact of maternal alcohol use on teen behavior would be secondary to exposure (of both caregiver and child) to a more stressful environment, rather than a function of maternal alcohol use *per se*. In support of this idea, Mulia et al. [49] found in a large urban sample of women that neighborhood disorder and stressful life events increased risk of problem drinking (mediated by psychological distress), which was not buffered by level of social support. Furthermore, several groups have found that maternal alcohol abuse is associated with child internalizing symptoms [12,34], which can include social avoidance-type behaviors such as the escape response that is modeled in the present study. Similar to these prior findings, we observed a significant positive correlation between the caregiver MAST total score (i.e., problem alcohol use) and the teen CBCL internalizing score.

Interestingly, the only variable in our data set that significantly predicted greater PSAP aggressive responding was conduct disorder/oppositional defiant disorder symptoms at age 14 years. These results are consistent with previous findings that a history of conduct disorder, antisocial personality disorder and/or violent behavior influences aggressive responding on the PSAP task [17,47,48]. The present finding therefore suggests that whereas childhood disruptive behavior patterns may predict aggressive tendencies on this task, PCE does not. Another potential limitation of this study is that ADHD was not specifically diagnosed. Given that one previous study [11] found a relationship between ADHD and aggressive responding on this task, it is possible that – in addition to conduct disorder/oppositional defiant disorder – ADHD could also influence responding on this task. Also, few of these teens have been assessed clinically for ADHD so few are receiving stimulant medication.

The present data show that PCE adolescents, in the context of a fictive social stressor, do *not* engage in greater aggressive (point subtraction) or appetitive (point/money-maintained) responding compared to non-exposed teens. Rather, the predominant response to experimental provocation was escape/avoidance from the stressor of having points taken away by an opponent. Although this preference could suggest an anxiogenic tendency in this group, teen anxiety symptom measures in this study were not robustly associated with escape responding. However, we correlated the total number of escape responses with indicators of anxiety and only one, the TRF DSM Affective Disorder total score, was significant (data not shown). Further, prior studies with the PSAP (which used small samples) have not indicated whether or not escape responding was associated symptomatic relationships. Thus, we remain cautious about this interpretation. Daily, high-dose PCE relative to no exposure has been shown to reduce social contact in adolescent (PND 30) male and female rats [52], young adult (PND 60–90) male rats [39], and adult (PND 120) male and female rats [52]. *Postnatal* cocaine exposure in rodents is also anxiogenic [6,28,67], although individual differences exist [56], and anxiety-like behaviors in these prior studies (e.g., rats not entering the open arms of an elevated plus maze) can be attenuated by pretreatment with the benzodiazepine anxiolytic diazepam but not the 5-HT_{1A} agonist buspirone [29,53].

One potential mechanism underlying this effect is that PCE may disrupt neurobiological responses or adaptations to exogenous stressors/challenges – including social and physical probes – disruptions that may not be evident when assessed under basal, non-stressed conditions [44,59,61,62]. Late adolescent/young adult (PND60) and adult (PND120) PCE rats (as defined by Spear & Brake [60]) exhibited greater emotional behavior [37], aggression [39], and immobility in response to physical stressors, such as forced swim or foot-shock, than non-exposed animals [9,30,31,52]. These data are consistent with other findings that chronic *postnatal* cocaine exposure is anxiogenic, i.e., promoting defensive or avoidant-like behaviors [6,28,69] that can be attenuated by alcohol [7] and anxiolytic drugs [29,51]. This could partly explain, through a negative reinforcement hypothesis such as anxiety alleviation, why cocaine abusers commonly use alcohol (e.g. [10]). Interestingly, the 5-HT_{1A} partial agonist gepirone decreased resident intruder-instigated aggressive behaviors in PCE rats [38] suggesting also that serotonin function underlying anxiety may be disrupted in these animals [5,32].

We recognize that numerous other prenatal and postnatal factors could have influenced teens' responding on this task. However, due to the extensive array of assessments in multiple domains of functioning in this longitudinal prospective study (including birth, age 6–7, and this age-14 wave), we were able to control for many of these effects. First, the effects of other prenatal drug exposures (e.g., nicotine, alcohol) were included in the

multivariate analyses and these factors did not account for significant variance in PSAP task performance.

Second, current adolescent drug use could potentially have contributed to the present findings. Recent analyses of this longitudinal data set at age 14 years indicate that the teens in this urban sample are using illicit drugs including high rates of cocaine, as well as alcohol, nicotine, marijuana, and opiates [24]. As noted earlier, data from biologic hair analysis (cocaine and opiates) and self-report (alcohol and other drugs) were obtained prospectively at the age-14 year visit. Although none of these factors accounted for significant variance in regression models that predicted PSAP performance, reliance on self-report for alcohol and drug other than cocaine and opiates outside the timeframe of biological detection could have underestimated actual use.

Third, the role of several important postnatal factors were assessed and controlled. For instance, home environment and parenting quality did not significantly influence PSAP responding, nor did the mother's postnatal cocaine use. This is an important, albeit complex issue. Although maternal separation itself may be a significant stressor, the mother's cocaine (and other drug) use during pregnancy may be a proxy for, or predictor of, poor home environment and parenting quality. Likewise, maternal separation – depending, in part, on the age of separation – could be a stressor (e.g., if child attachment was high) or a relief (i.e., if biological parenting was poor and adoptive parenting afforded social-emotional improvement). In fact, many children in this age-14 year cohort (19.2% of 432) had caregivers that were not the biological mother. To address both of these issues, presence/absence of the biologic mother, now or in the past, was controlled for in these analyses. In addition, because almost 20% of the sample was not being cared for by the biological mother, we also controlled for the home environment and parenting quality of the current caregiver.

In addition, measures of child physical and mental health, and maternal mental health and substance use were not significantly associated with PSAP responding. This suggests that these types of intra-familial chronic problems are unlikely to have produced an adverse background that influenced sensitivity to this experimental task. Furthermore, community (extra-familial) violence exposure – which we have found in this longitudinal cohort to be associated with other outcomes, such as reading achievement and IQ level [25] – did not explain significant variability in response to the PSAP task. Sex was a relatively weak but significant moderator of performance in that females were slightly more likely to engage in escape responding (Option C). However, after adjusting for the number of point subtractions (which could vary across subjects), sex did not significantly predict the number of escape responses per point subtraction. A limitation of the present study is that, due to the intensive battery of age 14-year assessments and lack of additional time, it was not feasible to manipulate provocation (point subtraction) frequency to determine teens' sensitivity to this variable.

In summary, among young adolescents with prenatal cocaine exposure (PCE) and whose mothers drank relatively higher levels of alcohol when the teens were 7 years old, a social provocation stressor led to behavioral preference for escape responding (negatively reinforced) rather than aggressive (retaliatory) or appetitive (money-reinforced) responding. In contrast, conduct disorder/oppositional defiant disorder symptoms were positively associated with greater aggressive responding. The findings are consistent with preclinical research showing that certain social stressors can produce greater submissive/anxious behavior rather than aggressive behavior in PCE relative to non-exposed rats during their juvenile, periadolescent and adult stages of development. These findings support the idea that PCE does not invariably produce more externalizing-type behaviors (e.g., aggression),

but may more likely engender developmentally specific internalizing behavior patterns (e.g., escape or avoidance). The finding that high levels of maternal alcohol use (postnatal, child age 7 years) also predicted greater escape responding at child age 14 years could reflect social modeling processes or other influences that require further study. This knowledge may help to diminish preconceptions and stigma about the consequences of PCE, and to assist prevention efforts with this adolescent population.

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Fig 1.

Effects of prenatal cocaine exposure (PCE) *versus* no exposure (NON) group and high *versus* low maternal alcohol use (at child age 7) group on the total number of escape (option C) responses in the Point Subtraction Aggression Paradigm (upper panel), and effects of these same two independent variables on the number of escape responses *per* point subtraction (lower panel). For each outcome measure, there were significant main effects of each grouping variable, but no significant interaction (see Table 3).

Table 1

Sample Characteristics.

	<u>N</u>	Mean or %	SD	Range
Caregiver				
Education (years)	416	12.2	2.0	2 – 21
Marital status (% married)	415	24.0	--	--
SESa	416	28.4	11.3	8 – 66
Age at 14-yr visit (years)	414	43.4	9.7	27.0 – 79.6
Primary caregiver (% mother)	416	81.0	--	--
Age at conception (years)	416	25.8	6.5	12 – 45
IQ	415	83.8	10.4	31 – 117
Teen				
Age at the 14-yr visit (years)	416	14.5	0.9	12.9 – 17.8
Sex (% male)	416	49.8	--	--
IQ	408	78.9	13.6	40 – 143

^aBased on Hollingshead Four-Factor Index of Social Status, 1975.

Table 2

Point Subtraction Aggression Paradigm Performance of Periadolescent Subjects, Grouped by Prenatal Cocaine Exposure (NON vs. PCE) and Level of Maternal Alcohol Use at Child Age 7 (Low vs. High).[¶]

Variable (units)	NON + Low Alcohol (<i>n</i> = 257)	NON + High Alcohol (<i>n</i> = 64)	PCE + Low Alcohol (<i>n</i> = 67)	PCE + High Alcohol (<i>n</i> = 17)
Option A (point/money) responses	3300 (945)	3233 (770)	3133 (776)	3101 (817)
Option B (aggressive) responses	192 (166)	232 (183)	206 (144)	204 (163)
Option C (escape) responses	312 (224)	368 (223)	381 (226)	541 (297)
Total responses	3789 (886)	3830 (691)	3717 (771)	3846 (683)
B responses per point subtraction	11.9 (10.0)	14.1 (11.3)	12.5 (8.6)	11.9 (9.5)
C responses per point subtraction	19.0 (13.5)	22.5 (13.9)	23.6 (14.60)	31.7 (17.2)
Points subtracted	16.6 (3.3)	16.7 (2.9)	16.8 (3.0)	16.9 (1.3)
Net earnings (\$)	4.30 (1.45)	4.19 (1.22)	4.50 (4.15)	3.99 (1.44)

[¶]Eleven children were missing maternal alcohol use data at age 7, and were not included in this analysis (total *N* = 405).

Table 3

Regression Model Predicting Point Subtraction Aggression Paradigm Option C (Escape) Responses: Predictor Coefficients and Significance Levels.

Predictor	Total Escape Responses ^a			
	<i>R</i> ² Change ^c	<i>p</i> value <i>R</i> ² Change	Standardized β ^d	<i>p</i> value ^d
Maternal Alcohol Intake at Child Age 7 Years (Low vs. High)	0.028	0.001	0.16	0.001
Number of Task Point Subtractions	0.020	0.006	0.13	0.007
Teen Gender (Male vs. Female)	0.011	0.036	0.09	0.078
Prenatal Cocaine Exposure (PCE)	0.027	0.005		
Persistent vs. None/Some			0.15	0.006
None vs. Some			0.04	0.417
Predictor	Escape Responses per Task Point Subtraction ^b			
	<i>R</i> ² Change ^c	<i>p</i> value <i>R</i> ² Change	Standardized β ^d	<i>p</i> value ^d
Maternal Alcohol Intake at Child Age 7 Years (Low vs. High)	0.029	0.001	0.14	0.007
Teen Gender (Male vs. Female)	0.013	0.025	0.10	0.042
Maternal Across-Pregnancy Alcohol Intake	0.011	0.042	0.09	0.077
Prenatal Cocaine Exposure (PCE)	0.026	0.006		
Persistent vs. None/Some			0.16	0.003
None vs. Some			0.01	0.875

^a *N* = 377

^b *N* = 376

^c Change in *R*² when variable entered model.

^d Standardized β and *p* value for variable in final model.