Published in final edited form as:

Drug Alcohol Depend. 2012 November 1; 126(1-2): 80–86. doi:10.1016/j.drugalcdep.2012.04.014.

Neurobehavioral Disinhibition Predicts Initiation of Substance Use in Children with Prenatal Cocaine Exposure

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Abstract

Background—In previous work we (Fisher et al., 2011) examined the emergence of neurobehavioral disinhibition (ND) in adolescents with prenatal substance exposure. We computed ND factor scores at three age points (8/9, 11 and 13/14 years) and found that both prenatal substance exposure and early adversity predicted ND. The purpose of the current study was to determine the association between these ND scores and initiation of substance use between ages 8–16 in this cohort as early initiation of substance use has been related to later substance use disorders. Our hypothesis was that prenatal cocaine exposure predisposes the child to ND, which, in turn, is associated with initiation of substance use by age 16.

Methods—We studied 386 cocaine exposed and 517 unexposed children followed since birth in a longitudinal study. Five dichotomous variables were computed based on the subject's report of substance use: alcohol only; tobacco only; marijuana only; illicit substances and any substance.

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Results—Cox proportional hazard regression showed that the 8/9 year ND score was related to initiation of alcohol, tobacco, illicit and any substance use but not marijuana use. The trajectory of ND across the three age periods was related to substance use initiation in all five substance use categories. Prenatal cocaine exposure, although initially related to tobacco, marijuana and illicit substance initiation, was no longer significant with ND scores in the models.

Conclusion—Prenatal drug exposure appears to be a risk pathway to ND, which by 8/9 years portends substance use initiation.

Keywords

neurodevelopmental disinhibition; substance use initiation; prenatal cocaine exposure

1. Introduction

Neurobehavioral disinhibition (ND) is a singular dimension of psychological dysregulation involving lack of behavior control and poor emotion modulation that has gained wide acceptance, including the prediction of substance use and substance use disorders (SUDs) in adolescents (Iacono et al., 2008). The construct is based on observations that many psychiatric disorders rarely occur in isolation but often occur in clusters. ND reflects a wide range of problems including impulsivity, reactive aggression, sensation seeking, excessive risk taking (Brook et al., 1992; Tarter et al., 1999), irritability, negative affect, difficult temperament (Blackson et al., 1999; Chasin and Barrera, 1993; Tarter et al., 1995), conduct disorder (CD), attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), anxiety, major depression disorder (MDD; Clark et al., 1999) and impaired executive function (Aytaclar et al., 1999; Giancola et al., 1996; Shoal and Giancola, 2001). Children with this constellation of problems often follow negative longitudinal trajectories associated with peer rejection, academic difficulties, delinquency, high rates of mental health, special education, residential care, and juvenile justice system involvement (Harden, 2004; Iacono et al., 2008). This dimension of vulnerability is related to substance use in adolescents (Tarter et al., 2004), early age onset of SUDs (Tarter et al., 2003), substance use in early adulthood (Kendler et al., 1994) and other problem behavior (McGue and Iacono, 2005). There is also evidence that it is highly heritable (Krueger et al., 2002; Young et al., 2009).

However, the literature varies with respect to which disorders are included as components on the ND spectrum. For some (Tarter et al., 2003), both internalizing and externalizing problems are included, whereas for others, the term is only applied to externalizing disorders (Krueger et al., 2002; Krueger and South, 2009). Executive function deficits and behavioral problems are included as part of a unidimensional disinhibition spectrum in some cases (Tarter et al., 2004) but not in others (Iacono, et al., 2008; Krueger and South, 2009).

Although ND has not been studied in children with prenatal cocaine exposure many of the components of ND mentioned above have been related to prenatal cocaine exposure. We (Lester and LaGasse, 2010) identified 42 published, prospective longitudinal follow-up studies of children with prenatal cocaine exposure representing 4,419 children from 14 different cohorts. This review suggested that there are unique effects of prenatal cocaine exposure on 4- to 13-year-old children. The largest number of prenatal cocaine exposure effects was in behavior problems (e.g. externalizing). In subsequent studies, prenatal cocaine exposure was related to teen substance use (Delaney-Black, et al 2011) and initiation of substance use (Frank, et al., 2011).

Maternal use of alcohol during pregnancy was related to ND at 10–12 years which, in turn, predicted later SUDs (Chapman, et al., 2007). We (Fisher et al., 2011) examined the

emergence in adolescence of ND in children with prenatal poly-substance exposure, including cocaine. We computed ND factor scores at three ages (8/9, 11 and 13/14 years) and used multivariate growth modeling and found that both prenatal substance exposure and early adversity predicted ND. The purpose of the current study was to determine the association between these ND factor scores and initiation of substance use in this cohort. We studied initiation of substance use rather than SUDs because initiation is thought to be related to SUDs in late adolescence and early adulthood. Earlier initiation of substances also increases the risk for neuropsychological disturbances and later problematic substance use (Carlin and O'Malley, 1996; Medina et al., 2007; Roselli et al., 2001; Rourke and Loberg, 1996; Schweinsburg et al., 2008; Solowij, 1998; Tapert et al., 2002). We examined the respective roles of prenatal cocaine exposure and ND in predicting the initiation of substance use. Our hypothesis was that prenatal cocaine exposure is related to ND, which, in turn, is associated with initiation of substance use by age 16.

2. Methods

2.1. Subjects

The Maternal Lifestyle Study is a multi-site (Detroit, Memphis, Miami and Providence), longitudinal study of children with prenatal cocaine exposure enrolled in 1993–1995. Maternal exclusion criteria included the following: younger than 18 years, psychosis or history of psychiatric institutionalization, or language barriers that prevented informed consent. Infant exclusion criteria included the following: multiple gestation, birth weight less than 501 grams, gestational age greater than 42 weeks, infant unlikely to survive in the judgment of the attending physician, chromosomal abnormalities, serious infection (e.g., rubella) or born outside of one of the four recruitment hospitals (for additional details see Lester et al., 2002). Meconium samples were collected in the nursery and analyzed at a central laboratory (Lester et al., 2001). Infants were selected to be in the prenatal cocaine exposure group (maternal report of cocaine or opiate use during pregnancy or confirmation of presumptive positive meconium screens for cocaine or opiate metabolites) or the non prenatal cocaine exposed group (maternal denial of cocaine or opiate use during the pregnancy and a negative meconium screen for cocaine and opiate metabolites). We refer to these two groups as “exposed” and “unexposed.” The exposed and unexposed infants were group matched on race, gender, and gestational age within site. Because most cocaine users also use other substances (e.g., alcohol, tobacco and marijuana) these substances were “controlled” by including them in both the exposed and unexposed groups. 1,388 mother-infant dyads (n=658 exposed, n=730 unexposed) were enrolled at 1-month with continued follow-up at 4, 8, 12, and 18 months, then annually starting at 24 months. The frequency of cocaine use per week for each trimester of pregnancy was based on maternal report and used to compute a measure of level of cocaine use (high, some and none; Lester et al., 2002). Children with prenatal opiate exposure (n=115) or with missing data (n=370) were excluded. Of those remaining, 903 subjects (exposed=386, unexposed=517) were evaluated for ND and initiation of substance use in this report.

2.2. Procedure

The study was approved by the Institutional Review Board at each site and written informed consent by parents and assent by the youth were obtained. Each site had a Certificate of Confidentiality from the National Institute on Drug Abuse. Here, we report data from annual follow-up visits at ages 8–16. Time required for each visit was approximately 3.5 hours for the child and 3 hours for the caregiver. At each visit, subjects were reimbursed for their time and effort, birthday celebrations were held for the child and transportation to the clinic was provided.

2.3. Measures

2.3.1. Neurobehavioral disinhibition—We employed ND scores computed at three assessment periods (8/9, 11, 13/14 years) using a strategy previously employed in a study involving the same sample (Fisher et al., 2011). ND was a composite score from the following established measures: (a) problem behaviors reported by caregivers on the Child Behavior Checklist (Achenback, 1991) using the standardized T-scores for total problem behaviors at ages 9, 11, and 13; (b) ODD, CD, ADHD, and MD counts reported by caregivers and child from the Diagnostic Interview Schedule for Children–IV (Shaffer et al., 2000) at ages 8, 11, and 14; and (c) delinquency summary scores for the number of child-reported crimes against people and acts of general and school delinquency from the Things That You Have Done (TYHD; Ingoldsby et al., 2006) at ages 9, 11, and 13. The ND score was computed by rescaling each indicator on a 0:1 ratio level continuous scale and then averaging. Using principal components factor analysis, we obtained a single-factor solution at each time point: Eigen values of 2.98, 3.27, and 3.25, respectively, explained over 50% of the variance. We initially attempted to create a single-factor solution using behavioral and executive functioning measures, however, this solution did not converge. We were able to compute separate factors for executive function at ages 9, 11 and 13 using the Spatial Working Memory and Stockings of Cambridge tests from the Cambridge Neuropsychological Test Automated Batteries (Luciana, 2003). Spatial working memory is measured by the temporary maintenance and manipulation of information such that the information may be used to complete a specified task such as reasoning and comprehension. Stockings of Cambridge measures executive function, specifically to detect deficits in planning efficiency such as impulsivity. We found that prenatal drug exposure was related to the behavioral factors but not to the executive function factors, thus we only included the behavioral factors in this report.

2.3.2 Substance use variables—Substance use was measured with the TYHD questionnaire yearly from ages 8–16. Use of each substance (alcohol, tobacco, marijuana, inhalants, crack/cocaine, ecstasy, heroin, methamphetamine, oxycodone, acetaminophen and hydrocodone, methylphenidate, alprazolam, over the counter medicine (e.g., cough medicine) was coded as yes or no. Five dichotomous variables were computed based on the subject's report of use at any age: alcohol only; tobacco only; marijuana only; illicit substances (any substance other than alcohol and tobacco); and any substance (illicit substances, alcohol or tobacco). Initiation of substance use in each of these categories was defined as age of first use.

2.3.3. Covariates—The effects of prenatal cocaine exposure on offspring are also influenced by exposure to substances other than cocaine and a confluence of interrelated familial and environmental factors. To determine if prenatal cocaine exposure is a significant contributor to or simply a marker for adverse outcome, we included the following covariates; prenatal exposure (yes or no) to other substances (tobacco, alcohol and marijuana), gender, birth weight, site and the following derived variables:

Socioeconomic status: Hollingshead Index of Social Position (Hollingshead, 1975) from income and occupation averaged over annual visits through 15 years.

Postnatal caregiver substance use: “Yes” if any use of cocaine, cigarettes, alcohol, or marijuana based on caregiver interview visits from 4 months to 15 years.

Primary caregiver changes: Number of changes in primary caregiver from 1 month to 15 years.

Domestic violence: “Yes” if caregiver reported any physical or sexual abuse at any visit through 15 years.

Community violence: Averaged scores of 2 questionnaires, (Martinez and Richters, 1993; Richters and Martinez, 1993) the child-report, Things I’ve Seen and Heard at ages 8, 12 and 15 and the caregiver-report Survey of Exposure to Community Violence at ages 9, 12, and 15.

Home environment: Quality of the home based on averaged scores from the Home Observation Measurement of the Environment (HOME; Caldwell and Bradley, 1984) administered at 10 months, then at 5 ½, 9 and 13-year visits in the home.

Caregiver psychological distress: Average number of psychological symptoms above the clinical cut-off on the Brief Symptom Inventory (Derogotis, 1992) administered to the caregiver at 4 and 30 months and 5½, 9 and 11-year visits.

Caregiver depression: Averaged scores on the caregiver-report Beck Depression Inventory (BDI; Beck, 1978) at 4 and 30 months and 4, 5½, 7, 9, 11, 13 and 15-year visits.

Child abuse: “Yes” if a child protective services case was opened based on evidence of physical and/or sexual abuse at any age from 1 month to 15 years.

Early puberty: Tanner score (Costello et al., 2007) of 4 or 5 before age 12 for boys or age 11 for girls.

2.4. Statistical Analysis

Categorical variables (e.g., race, gender) were described as percentages. Continuous variables (e.g., birth weight, BDI, ND scores) were described as means and standard deviations. Comparisons of these characteristics were conducted by logistic regression for categorical variables or general linear models (GLM) for continuous variables. Mixed modeling was used to evaluate the trajectory of ND scores from 8/9 thru 13/14 by prenatal cocaine exposure. The nesting structure of subjects in study sites was taken into account. It is assumed in this model that the ND score changed smoothly over this period of time.

Cox proportional hazard regression was used to determine associations between prenatal cocaine exposure and ND (at 8/9 years or as a time varying trajectory) and initiation of substance use from 8 to 16 years. For each substance use category, the model had three steps: first, prenatal cocaine exposure alone; second; ND was included to examine potential mediation of exposure effects; third, covariates were added to examine if effects were maintained with confounding variables.

Covariates were selected based on conceptual considerations, published literature, and statistical evidence. *A priori* covariates included gender, prenatal alcohol, marijuana and tobacco exposure, and study site. The following additional covariates were included in stepwise selection with entry criterion =0.99 and criterion to remain in the model =0.995 (Shtatland et al., 2005): birth weight, SES, primary caregiver changes, postnatal caregiver use of tobacco, alcohol, and marijuana, community and domestic violence, home environment, caregiver depression and psychological distress, early puberty and child abuse. We tested the interaction of prenatal cocaine exposure and early puberty with gender, but they were not significant and excluded from further models.

Akaike Information Criterion (AIC) was used to determine the best sets of covariates for specific substance use categories. AIC takes into consideration both the statistical goodness

of fit and the number of parameters required to achieve this particular degree of fit by imposing a penalty for increasing the number of covariates in the model. The final Cox models were fit with specification of categorical covariates. All statistical analyses were conducted with SAS (version 9.1.3; SAS Institute, Cary, NC; Shtatland et al., 2005). Differences for all tests were considered significant at $p < .05$.

3. Results

3.1. Subject characteristics

Sample characteristics for the 903 included subjects (Table 1) showed that compared to mothers of children in the unexposed group, mothers in the exposed group were older, single, lower SES, receiving Medicaid, less educated, had greater psychological distress and used more alcohol, tobacco and marijuana prenatally. They also used more cocaine, tobacco, alcohol and marijuana postnatally. Compared to children in the unexposed group, children in the exposed group had more primary caregiver changes, were more often exposed to domestic and community violence, were more likely to have been abused and had lower birth weight.

3.2. Substance use

Substance use from age 8 to 16 for each substance and substance use category is shown in Table 2. Statistical comparisons were not conducted for substances with low prevalence rates. More children in the exposed group used tobacco, marijuana and illicit substances than children in the unexposed group. None of the comparisons by level of cocaine exposure (high, some, none) were statistically significant in these analysis or in any of the analyses reported below.

3.3 Neurobehavioral Disinhibition

Results of longitudinal analysis showed that the trajectory of ND scores was significantly higher in the exposed than in the unexposed group ($P=0.002$). Univariate analysis also showed the mean ND scores were higher in the exposed than in the unexposed group at each age (age 8/9, $P=.041$; age 11, $P=.030$ and age 13/14, $P=.003$).

3.4 Initiation of Substance Use

Results from the Cox models are shown in Table 3.

Alcohol—There was no association between prenatal cocaine exposure and alcohol initiation by age 16. When added to the model, ND at 8/9 years was related to alcohol initiation. With additional covariates, the association between 8/9 year ND scores and alcohol initiation remained. For every unit increase in 8/9 year ND scores, there was a 2-fold risk for alcohol initiation. Exposure to community violence was related to alcohol initiation ($HR=1.13$; $CI=1.07-1.19$).

In the analysis with ND as a time varying covariate (trajectory) added to the cocaine exposure model, trajectories of ND were associated with alcohol initiation. When additional covariates were added to the model, the association between alcohol initiation and the trajectory of ND remained. For each unit increase in ND there was a 5 fold risk for alcohol initiation. Alcohol initiation was also related to exposure to community violence ($HR=1.10$, $CI=1.06-1.13$) and early onset of puberty ($HR=1.28$, $CI=1.10-1.49$).

Tobacco—Prenatal cocaine exposure was associated with tobacco initiation by age 16. When the 8/9 year ND score was added to the model, the exposure effect approached significance ($P=.058$) and ND was related to tobacco initiation. With additional covariates,

the association between 8/9 year ND scores and tobacco initiation remained. For every unit increase in 8/9 year ND scores, there was a 6 fold risk for tobacco initiation. Tobacco initiation was also related to exposure to community violence (HR=1.18; CI=1.08–1.28) and child abuse (HR=2.72; CI=1.57–4.71).

In the analysis with prenatal cocaine exposure and the trajectory of ND, both exposure and the trajectory of ND were associated with tobacco initiation by age 16. With additional covariates, the exposure effect did not remain but the association between the trajectory of ND and tobacco initiation was maintained. For each unit increase in the trajectory of ND, there was a 20 fold risk for tobacco initiation. Tobacco initiation was also related to exposure to community violence (HR=1.13, CI= 1.07–1.20) and child abuse (HR=2.55, CI= 1.79–3.63).

Marijuana—Prenatal cocaine exposure was associated with marijuana initiation by age 16. When ND at 8/9 was added to the model, both the exposure effect and ND was associated with marijuana initiation. When covariates were added neither exposure nor ND was related to marijuana initiation. Marijuana initiation was related to boys (HR=1.43, CI= 1.06–1.94) and exposure to community violence (HR=1.19, CI= 1.11–1.27).

In the analysis with prenatal cocaine exposure and the trajectory of ND, both exposure and the trajectory of ND were associated with marijuana initiation by age 16. When covariates were added, the association between the trajectory of ND and marijuana initiation was maintained. For each unit increase in the trajectory of ND, there was a 7.4 fold risk for marijuana initiation. Marijuana initiation was also related to boys (HR=1.45, CI=1.21–1.74), prenatal exposure to marijuana (HR=1.26, CI= 1.02–1.56), exposure to community violence (HR=1.16, CI=1.11–1.21) and early puberty (HR=1.25, CI=1.03–1.53).

Illicit Substance Use—Prenatal cocaine exposure was associated with illicit substance initiation by age 16. When ND at 8/9 was included, the exposure effect remained and the ND score was associated with illicit substance initiation. With the addition of covariates, illicit substance use was only related to the 8/9 year ND score. For every unit increase in the ND score at 8/9, there was a 4½ fold increase in the hazard of illicit substance initiation. Illicit substance initiation was also related to boys (HR=1.43, CI=1.07–1.90) and exposure to community violence (HR=1.17; 1.09–1.24).

In the analysis with prenatal cocaine exposure and the trajectory of ND, the exposure effect remained and the trajectory of ND was associated with illicit substance initiation by age 16. With covariates, illicit substance initiation was only related to the trajectory of ND. For every unit increase in the trajectory of ND score, there was a 10.2 fold risk for illicit substance initiation. Illicit substance initiation was related to boys (HR=1.46; 1.23–1.74), exposure to community violence (HR=1.14; 1.09–1.18) and early puberty (HR=1.22; 1.01–1.47).

Any Substance Use—There was no association between prenatal cocaine exposure and any substance initiation. ND at 8/9 was related to any substance initiation when added to the model. With the addition of covariates, the association between ND at 8/9 and any substance initiation remained. For every unit increase in the ND score at 8/9, there was a 2 fold risk for any substance initiation. Any substance initiation was related to exposure to community violence (HR=1.13, CI=1.08–1.18) and early puberty (HR=1.27, CI=1.01–1.58).

In the analysis with prenatal cocaine exposure and the trajectory of ND, the trajectory of ND was related to any substance initiation. This effect remained with the addition of covariates. For every unit increase in the trajectory of ND there was a 4.8 fold risk for any substance

initiation. Any substance initiation was related to exposure to community violence (HR=1.09, CI=1.06–1.13) and early puberty (HR=1.26, CI=1.09–1.44).

4. Discussion

We examined the role of ND at 3 ages between ages 8 and 14 predicting substance use initiation in a longitudinal cohort of children with prenatal cocaine exposure. ND scores were higher in children with prenatal cocaine exposure and appear to mediate relations between prenatal cocaine exposure and initiation of substance use by age 16. Prenatal cocaine exposure was initially related to tobacco, marijuana and illicit substance initiation. However, when ND and covariates were included, prenatal cocaine exposure effects were no longer significant and ND scores remained significant in virtually all of the models. Thus, prenatal drug exposure appears to be a risk pathway to ND, which portends substance use initiation which has been related to increased risk of later drug problems (Anthony and Petronis, 1995; Korhonen et al., 2008; Kramer et al., 2009; Kuperman et al., 2005), teen (Korhonen et al., 2008), family (Doherty et al., 2007; Kramer et al., 2009; Kuperman et al., 2005) and community problems (Fothergill and Ensminger, 2006; MacKay et al., 2009; Whitesell et al., 2007).

ND predicted initiation of substance use in two ways. Using the 8/9 year score, ND was related to the initiation of alcohol, tobacco, illicit and any substance use but not marijuana use. The trajectory of ND across the three age periods was related to substance use initiation in all five substance use categories. The finding that ND at 8/9 is related to substance initiation could have important implications for preventive intervention as it suggests that these children can be identified earlier than previously reported. However, it is also important to recognize that the hazard ratios were two to three times higher for the trajectory analysis compared to the use of the 8/9 year score. Although it may not seem surprising that prediction increases with more information, our findings suggest that ND is a relatively stable “trait” that emerges in 8–9 year olds.

Covariates were also related to substance initiation. Exposure to community violence was related to substance initiation in all five substance categories. Early puberty was related to four of the five categories. Marijuana and illicit substance use were more common in boys, and child abuse was related to tobacco initiation.

We know that social environmental and biological factors contribute to adolescent substance use (Iacono et al., 2008; Ridenour et al., 2009; Zucker et al., 2011). Effects of exposure to community violence and child abuse have been reported in the adolescent substance use literature and been related to developmental outcome in cocaine exposed children. In our previous report (Fisher et al., 2011) prenatal exposure and environmental adversity were independent predictors of ND. Keys et al. (2007) found that contextual risk was related to ND. Biological factors including male gender and early puberty are also predictors of adolescent substance use. We suggest that prenatal cocaine exposure contributes to an underlying vulnerability in ND, further amplified by social environmental and biological factors that could increase the liability for SUDs.

As noted, there is evidence that ND is highly heritable (Krueger et al., 2002; Young et al., 2009) and it is possible that prenatal cocaine exposure is simply another marker for genetic liability. However, cocaine also affects two neural systems that have been implicated in adolescence as part of normal developmental processes, risk taking, addiction liability and behavior disorders. The two neural systems, reward circuitry in the brain and prefrontal cortex, are represented by our behavioral and executive function factors, respectively.

Risk-taking during adolescence is thought to be due to the interaction between dynamic socio-emotional and cognitive control networks that develop more slowly and over a longer period of time (Steinberg, 2007). Increased reward sensitivity and reward seeking that accompanies heightened risk taking in adolescence is related to changes in patterns of dopaminergic activity around puberty. Cocaine also affects dopaminergic reward circuitry in the brain in the nucleus accumbens (Nestler, 2005) in the ventral striatum and this system has been related to addiction liability and behavior disorders. Risk taking declines in the emerging adult as the capacity for self regulation improves due to structural and functional changes in prefrontal cortex. For example, dorsolateral prefrontal cortex is involved in cognitive control, impulsivity and has been related to disinhibitory disorders in adolescents (Iacono et al., 2008) and damage to the prefrontal cortex is one of the effects of drugs on the adult brain (Goldstein and Volkow, 2002).

Thus, ND can occur through “bottom up” (increased sensitivity to reward) and “top down” (failure of prefrontal cortex inhibitory control) mechanisms (Iacono et al., 2008). In our previous work with this sample the effects of prenatal exposure on the executive factor were mediated through the behavioral factor suggesting that exposed youth who enter adolescence with behavior problems are most likely to experience executive function difficulties. Our ND findings could suggest that prenatal cocaine exposure further increases reward sensitivity (behavior factor) which in turn decreases prefrontal inhibitory control (executive function factor). The fact that the behavioral but not the executive function factor was related to prenatal cocaine exposure invites speculation that exposed children at this age, as they transition to adolescence, are being more influenced by “bottom up” than “top down” mechanisms. The effects of prenatal cocaine exposure on reward sensitivity function could result in a protracted timetable in the development of self regulation processes, increasing the period of vulnerability for risk taking behavior including liability for SUDs.

There are several limitations to this study. We did not measure genetic factors. We did not find effects for level of prenatal cocaine exposure probably because there were too few subjects with high levels of exposure who also used substances. We did not measure other dimensions of ND that have been used by others including, temperament, sensation seeking, risk taking and other executive function tests.

These limitations notwithstanding, this is a unique cohort that has been followed since birth in a prospective longitudinal design with a bioassay for prenatal cocaine exposure and thorough measurement of potential covariates. It is critical that these young adolescents continue to be followed to determine liability for SUDs in the later years. Finally, this study could have treatment implications and target children on the ND spectrum (perhaps as early as 8/9 years) in an effort to prevent substance use and SUDs, perhaps by helping them learn executive function skills to make less harmful choices.

Acknowledgments

This work was supported by NIH grants:

Supported by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network and an interinstitute agreement with the National Institute on Drug Abuse (NIDA) through cooperative agreements: U10-DA-024117-01, U10-HD-21385 (to SS), U10-DA-024128-06, U10-HD-2786 (to HSB), U10-DA-024119-01, U10-HD-27904 (to BML), and U10-DA-024118-01, U10-HD-21397 (to CRB); NICHD contract N01-HD-2-3159 (to BML).

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Table 1**Population Characteristics in Exposed and Unexposed Groups**

Variables	Exposed n = 386	Unexposed n = 517	p
Race: Black, n (%)	320 (82.9)	412 (79.7)	0.516
Maternal age: 18 – 25 years, n (%)	76 (19.7)	267 (51.6)	<0.001
Marital status: single, n (%)	348 (90.4)	393 (76.0)	<0.001
Hollingshead Index of Social Position, mean (SD)	27.1 (7.8)	30.2 (8.9)	<0.001
Medicaid, n (%)	337 (87.3)	411 (79.5)	0.002
Education < 12 years, n (%)	195 (50.5)	162 (31.3)	<0.001
Prenatal alcohol use, n (%)	294 (76.2)	258 (49.9)	<0.001
Prenatal tobacco use, n (%)	316 (81.9)	149 (28.8)	<0.001
Prenatal marijuana use, n (%)	155 (40.2)	49 (9.5)	<0.001
Postnatal caregiver cocaine use, n (%)	105 (27.2)	6 (1.2)	<0.001
Postnatal caregiver alcohol use, n (%)	338 (87.6)	415 (80.3)	0.004
Postnatal caregiver tobacco use, n (%)	329 (85.2)	264 (51.1)	<0.001
Postnatal caregiver marijuana use, n (%)	145 (37.6)	110 (21.3)	<0.001
Primary caregiver changes, mean (SD)	1.97 (1.96)	0.59 (1.28)	<0.001
Domestic violence, n (%)	111 (28.8)	105 (20.3)	0.003
Community violence, mean (SD)	4.41 (2.43)	3.61 (2.27)	<0.001
Home environment, mean (SD)	36.0 (5.3)	36.2 (5.7)	0.594
Caregiver psychological distress, mean (SD)	0.53 (0.41)	0.48 (0.39)	0.045
Caregiver depression, mean (SD)	9.52 (5.42)	9.17 (5.55)	0.343
Child abuse, n (%)	34 (9.0)	21 (4.2)	0.003
Child gender: male, n (%)	202 (52.3)	259 (50.1)	0.506
Child gestational age, wk; mean (SD)	36.1 (4.0)	36.3 (4.0)	0.460
Child birth weight, g; mean (SD)	2568 (747)	2678 (865)	0.046
Child head circumference, cm; mean (SD)	32.0 (2.8)	32.2 (3.2)	0.225
Child birth length, cm; mean (SD)	46.5 (4.7)	47.0 (5.2)	0.102
Early puberty, Tanner 4 (boy<12 yr, girl<11 yr), n (%)	100 (27.2)	124 (25.1)	0.493

NOTE: % of categorical variables calculated in available data

Table 2

Comparison of Substance Use Category in Exposed and Unexposed Groups

Substance Category	Unexposed n = 517	Exposed n = 386	p
Alcohol	201 (38.8%)	146 (37.8%)	0.701
Tobacco	58 (11.2%)	61 (15.8%)	0.046
Marijuana	94 (18.1%)	93 (24.0%)	0.026
Illicit Substance	103 (19.9%)	108 (27.9%)	0.004
Any Substance	244 (47.1%)	183 (47.4%)	0.920
Heroin	-	-	-
Cocaine	-	3 (0.8%)	-
LSD	-	-	-
Ecstasy	3 (0.6%)	8 (2.1%)	-
Methamphetamine	-	1 (0.3%)	-
Oxycontin	1 (0.2%)	3 (0.8%)	-
Vicodin	12 (2.4%)	9 (2.4%)	-
Ritalin	1 (0.2%)	2 (0.5%)	-
Xanax	3 (0.6%)	4 (1.1%)	-
OTC (Cold Medicine)	8 (1.6%)	2 (0.5%)	-
Inhalant	15 (3%)	22 (5.9%)	-

Table 3
Effects of Prenatal Cocaine Exposure and Behavioral Disinhibition on Initiation of Substance Use from 8 to 16 Years

Hazard Ratio (95th CI)	Alcohol	Tobacco	Marijuana	Illicit Substances	Any Substance
Exposure	Step 1	Step 1	Step 1	Step 1	Step 1
	0.97 (0.79-1.21)	1.46 (1.02-2.09)	1.39 (1.04-1.69)	1.49 (1.13-1.95)	1.03 (0.85-1.25)
Exposure	Step 2	Step 2	Step 2	Step 2	Step 2
	0.95 (0.77-1.18)	1.42 (0.99-2.03)	1.35 (1.01-1.80)	1.44 (1.10-1.89)	1.01 (0.83-1.22)
Behavioral Disinhibition 8/9 yr	4.51 (1.93-10.55)	18.79 (4.56-77.46)	8.82 (2.79-27.88)	11.88 (4.02-35.14)	5.22 (2.42-11.24)
	Step 3 ^d	Step 3 ^c	Step 3 ^e	Step 3 ^g	Step 3 ⁱ
Exposure	0.87 (0.66-1.15)	1.08 (0.68-1.72)	1.04 (0.73-1.49)	1.11 (0.79-1.56)	0.94 (0.73-1.21)
Behavioral Disinhibition 8/9 yr	3.32 (1.22-9.06)	7.00 (1.21-40.52)	3.06 (0.80-11.67)	5.49 (1.57-19.20)	2.96 (1.18-7.46)
Exposure	Step 2	Step 2	Step 2	Step 2	Step 2
	0.91 (0.80-1.05)	1.34 (1.06-1.69)	1.31 (1.10-1.56)	1.42 (1.20-1.67)	0.98 (0.86-1.10)
Trajectory of Behavioral Disinhibition	10.59 (6.38-17.56)	55.08 (23.95-126.70)	25.64 (13.37-49.17)	27.81 (15.07-51.29)	11.26 (7.09-17.89)
	Step 3 ^b	Step 3 ^d	Step 3 ^f	Step 3 ^h	Step 3 ^j
Exposure	0.85 (0.71-1.01)	1.05 (0.78-1.41)	1.08 (0.87-1.34)	1.16 (0.94-1.42)	0.94 (0.80-1.10)
Trajectory of Behavioral Disinhibition	5.99 (3.34-10.74)	21.22 (7.81-57.65)	8.34 (3.98-17.50)	11.19 (5.60-22.35)	5.84 (3.41-10.01)

Note: Step 1 of the trajectory analyses of behavior disinhibition is the same as Step 1 of the 8/9 year analyses and is not repeated.

^a Adjusted for gender, alcohol, tobacco and marijuana exposures, SES, community violence, home environment, caregiver depression, child abuse, early puberty, site.

^b Adjusted for gender, alcohol, tobacco and marijuana exposures, community violence, home environment, early puberty.

^c Adjusted for gender, alcohol, tobacco and marijuana exposures, community violence, child abuse, early puberty, site.

^d Adjusted for gender, alcohol, tobacco and marijuana exposures, community violence, child abuse, early puberty, site.

^e Adjusted for gender, alcohol, tobacco and marijuana exposures, community violence, home environment, early puberty, site.

^f Adjusted for gender, alcohol, tobacco and marijuana exposures, community violence, early puberty, site.

^g Adjusted for gender, alcohol, tobacco and marijuana exposures, community violence, home environment, early puberty, site.

^h Adjusted for gender, alcohol, tobacco and marijuana exposures, community violence, early puberty, site.

ⁱ Adjusted for gender, alcohol, tobacco and marijuana exposures, SES, community violence, home environment, child abuse, early puberty, site.

^jAdjusted for gender, alcohol, tobacco and marijuana exposures, community violence, child abuse, early puberty, site.