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KEY WORDS
prenatal substance exposure, cocaine, neurobehavioral dysregulation, behavior problems

ABBREVIATIONS
SEM—structural equation modeling
SES—socioeconomic status
NNNS—NICU Network Neurobehavioral Scale
IBQ—Infant Behavior Questionnaire
CBCL—Child Behavior Checklist

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WHAT'S KNOWN ON THIS SUBJECT: Follow-up studies relating prenatal cocaine and other substance exposures to behavioral problems during childhood typically use a behavioral teratology model, enabling us to determine not only whether there is a unique drug effect but also the magnitude of the effect.

WHAT THIS STUDY ADDS: We used SEM to test a developmental model relating prenatal cocaine and other substance exposure to later behavior problems. The findings demonstrate how prenatal substance exposure affects child outcome and have implications for early identification and prevention.

abstract

OBJECTIVE: The objective of this study was to test a developmental model of neurobehavioral dysregulation relating prenatal substance exposure to behavior problems at age 7.

METHODS: The sample included 360 cocaine-exposed and 480 unexposed children from lower to lower middle class families of which 78% were black. Structural equation modeling was used to test models whereby prenatal exposure to cocaine and other substances would result in neurobehavioral dysregulation in infancy, which would predict externalizing and internalizing behavior problems in early childhood. Structural equation models were developed for individual and combined parent and teacher report for externalizing, internalizing, and total problem scores on the Child Behavior Checklist.

RESULTS: The goodness-of-fit statistics indicated that all of the models met criteria for adequate fit with 7 of the 9 models explaining 18% to 60% of the variance in behavior problems at age 7. The paths in the models indicate that there are direct effects of prenatal substance exposure on 7-year behavior problems as well as indirect effects, including neurobehavioral dysregulation.

CONCLUSIONS: Prenatal substance exposure affects behavior problems at age 7 through 2 mechanisms. The direct pathway is consistent with a teratogenic effect. Indirect pathways suggest cascading effects whereby prenatal substance exposure results in neurobehavioral dysregulation manifesting as deviations in later behavioral expression. Developmental models provide an understanding of pathways that describe how prenatal substance exposure affects child outcome and have significant implications for early identification and prevention. *Pediatrics* 2009;124:1355–1362

Follow-up studies relating prenatal cocaine and other substance exposures to behavioral problems during childhood typically use a behavioral teratology model.[1–4] The goal here is to isolate the effects of a teratogen by controlling for effects of potential confounding variables through study design such as matching and/or statistics in which confounding variables are covaried. The variance in outcome explained by the confounding variables is essentially removed from the analysis, and the leftover unexplained variance is attributed to the teratogen. For example, we found effects of prenatal cocaine exposure on trajectories of behavior problems from 3 to 7 years independent of the effects of prenatal exposure to alcohol and tobacco, as well as other potentially confounding variables.[5] The behavioral teratology model is critically important because it enables us to determine not only whether there is a unique drug effect (ie, drugs affect outcome when confounding factors are controlled) but also the magnitude of the drug effect (ie, variability in the outcome measure explained by the drug alone).

A limitation of the behavioral teratology approach, however, is that it does not lend itself to the study of the developmental processes that lead from exposure to developmental outcome. In addition to direct drug effects, there may be indirect effects that suggest how factors mediate the relationship between teratogenic effects and developmental outcome. In a developmental model, effects that are removed as confounding variables can be studied as factors that explain more of the variability in developmental outcome in the presence of teratogenic effects. In other words, these factors are included rather than controlled or removed. In addition, other factors that are hypothesized to be involved in these developmental models can be included. Statistical techniques such as path analysis or structural equation modeling (SEM) are often used to study these pathways. In previous work, path models showed that growth deficits associated with prenatal cocaine exposure are mediated, in part, by gestational age.[6] In addition to direct effects of prenatal cocaine exposure on IQ, indirect effects are mediated by head circumference, child behavior, and the home environment.[7] In our work, the relationship between prenatal cocaine exposure and hypertension was mediated by BMI.[8]

In this study, we used SEM to test a developmental model relating prenatal cocaine and other substance exposure to behavior problems at age 7. The primary hypothesis was that prenatal exposure to cocaine and other substances would result in neurobehavioral dysregulation in infancy (ie, problems with arousal and reactivity), which would predict externalizing and internalizing behavior problems in childhood. Externalizing and internalizing behavior problems are part of the neurobehavioral disinhibition profile that includes cognitive, emotional, and behavioral disturbances.[9] This profile reflects diminished inhibitory control and is related to early onset of substance use.[9–11] In this study, we were interested in the behavioral antecedents of neurobehavioral disinhibition; therefore, we predicted that children who showed signs of neurobehavioral dysregulation at 1 month would have a difficult temperament at 4 months, leading to behavior problems at 3 and 7 years of age. Our long-term goal is to delineate developmental pathways in which children with prenatal cocaine exposure are at increased risk for adolescent substance use.

METHODS

Mothers and their infants were enrolled in the Maternal Lifestyle Study, a multisite, longitudinal study of prenatal cocaine exposure conducted at 4 centers (Wayne State University, University of Tennessee at Memphis, University of Miami, and Brown University). Each participating center had approval for the study from the institutional review board and a certificate of confidentiality from the National Institute on Drug Abuse. Between May 1993 and 1995, mothers at these centers were enrolled into the study within 24 hours after delivery. Initial screening included the mother's labor and delivery chart, newborn admission chart, and a meconium sample. A substance use questionnaire that addressed the mother's use of nicotine, alcohol, marijuana, cocaine, opiates, and other illicit substances was administered by research staff who were trained and certified in the reliable administration of the interview. Exposure was determined by mother's verbal admittance of using cocaine during pregnancy and/or a positive meconium assay for cocaine metabolites including gas chromatography/mass spectrometry confirmation. Nonexposed children were born to mothers who denied cocaine use, confirmed by negative meconium test results. All demographic data were collected at the time of the infant's birth.

As previously reported,[12] participants for the longitudinal follow-up were recruited at a 1-month visit. The sample included a cohort of exposed infants ($n = 658$) who were matched within each site with a group of nonexposed comparison infants ($n = 730$) by gestational age categories (<32, 33–36, and >36 weeks) and child gender, race, and ethnicity. Of the 1388 infants recruited, 955 had complete 7-year behavioral outcome data. Infants with prenatal opiate exposure ($n = 115$) were excluded because they constituted $<10\%$ of the original sample and differed from the rest of the sample

TABLE 1 Neonatal Characteristics of Infants Included and Excluded From the Study by Cocaine Exposure

Characteristic	Cocaine Exposed			Comparison		
	Included ($n = 360$)	Excluded ($n = 183$)	*P*	Included ($n = 480$)	Excluded ($n = 250$)	*P*
Gestational age, mean (SD), wk	36.0 (4.1)	36.2 (3.7)	.640	36.3 (4.1)	36.4 (4.0)	.663
Birth weight, mean (SD), g	2546 (780)	2587 (656)	.544	2675 (881)	2699 (835)	.719
Length, mean (SD), cm	46.3 (5.0)	46.6 (3.8)	.385	44.0 (5.3)	47.20 (5.1)	.547
Head circumference, mean (SD), cm	31.9 (2.9)	32.1 (2.7)	.513	32.2 (3.2)	32.3 (3.0)	.547
Apgar at 1 min, median (range)	8 (1–10)	8 (1–10)	.033[a]	8 (0–9)	8 (1–9)	.269
Apgar at 5 min, median (range)	9 (3–10)	9 (2–10)	.441	9 (4–10)	9 (1–10)	.118
Male, mean (SD), %	190 (52.8)	98 (53.6)	.864	231 (48.1)	114 (45.6)	.517
Firstborn, mean (SD), %	31 (8.6)	19 (10.4)	.500	134 (27.9)	89 (35.6)	.032[a]

on demographic characteristics (data not shown). The final sample for this study included 360 cocaine-exposed and 480 unexposed children who were followed from 1 month to 7 years of age. There were no differences in neonatal characteristics between infants who were included and excluded from the current sample except for differences in Apgar scores at 1 minute among the cocaine-exposed group and more firstborn children in the comparison group excluded than included (Table 1). For maternal characteristics (Table 2), there were fewer black mothers in the cocaine-exposed excluded than included group, more mothers in the 26- to 36-year age range in the cocaine-exposed included group than excluded group, and a higher percentage of families in the low socioeconomic status (SES) range in the included than the excluded comparison group.

Measures

Medical characteristics were collected at birth (Table 1). Caregiver age, race, marital status, education level, and Medicaid insurance status were collected at 1 month. SES was measured using the Hollingshead Index of Social Position[13,14] at 7 years. Each of the 4 exposure substances (cocaine, tobacco, alcohol, and marijuana) was converted to a categorical scale (yes/no) to indicate use of the substance during pregnancy. The NICU Network Neurobehavioral Scale (NNNS)[15] provides an assessment of infant neurologic, behavioral, and stress/abstinence function. The NNNS includes 13 summary scales with adequate psychometric properties.[16] The NNNS was administered at 1 month in the hospital by a certified examiner who was masked to exposure status of the newborn. A modified version of the Infant Behavior Questionnaire (IBQ)[17] was administered as a caregiver-report measure of infant temperament at 4 months.* The IBQ summary scales included distress to novelty and distress to limitations to represent difficult temperament.

The Child Behavior Checklists (CBCL) for ages 2 to 3 and 4 to 18 are 99- and 118-item questionnaires, respectively, that assess child behavior by using caregiver report.[18,19] Broadband scales for internalizing, externalizing, and total problems are derived. Test–retest reliability ranged from .74 to .96, and construct validity ranged from .84 to .90. The CBCL was administered to the caregiver at 3 and 7 years as well as the child's teacher, who was unaware of the child's drug exposure status, at 7 years.

TABLE 2 Characteristics of Mothers Included and Excluded From the Study by Cocaine Exposure

Characteristic	Cocaine Exposed, *n* (%)			Comparison, *n* (%)		
	Included ($n = 360$)	Excluded ($n = 183$)	*P*	Included ($n = 480$)	Excluded ($n = 250$)	*P*
Black race	299 (83.1)	136 (74.3)	.016[a]	381 (79.4)	189 (75.6)	.242
Age 26–36 y	255 (70.8)	111 (60.7)	.017[a]	204 (42.5)	90 (36.0)	.089
Marital status: single	326 (90.8)	158 (86.3)	.111	356 (74.2)	185 (74.3)	.970
Insurance: Medicaid	313 (86.9)	158 (86.3)	.844	374 (77.9)	193 (77.2)	.825
Education less than high school	181 (50.3)	92 (50.3)	.999	155 (32.4)	72 (28.8)	.325
Hollingshead SES: low-V	93 (27.6)	50 (29.2)	.697	109 (22.9)	37 (15.2)	.015[a]
Prenatal drug use						
Alcohol	274 (76.1)	135 (73.8)	.550	234 (48.8)	128 (51.2)	.530
Tobacco	293 (81.4)	157 (85.8)	.198	143 (29.8)	68 (27.2)	.464
Marijuana	143 (39.7)	82 (44.8)	.255	45 (9.4)	26 (10.4)	.657

Statistical Analysis

The statistical analysis was a 2-step process using Mplus SEM software.[20] First, latent variables, which are unobserved constructs that represent statistically related observed variables, were developed to measure prenatal substance exposure, neurobehavioral dysregulation on the NNNS, difficult temperament on the IBQ, and behavior problems on the CBCL. Second, SEM was used to develop models that help examine the relationship between the latent variables, and goodness-of-fit statistics were used to test the adequacy of each model. The primary model tested was that prenatal substance exposure results in disorganization at 1 month (NNNS), which, in turn predicts difficult temperament at 4 months (IBQ), behavior problems at ages 3 and 7 (CBCL). SES was included in the model, and study site, birth weight, and out-of-home placement were tested for inclusion. Models were

*Modifications, approved by M.K. Rothbart, included simplification of language for the Maternal Lifestyle Study population and reduction of response scale to 5 points.

TABLE 3 Summary of Structural Equation Models Predicting Child Behavior at Age 7 With Prenatal Drug Exposure ($N = 840$; 360 Cocaine Exposed and 480 Comparison)

Paths in the Model	Path Coefficients in Each Model								
	Caregiver Report			Teacher Report			Caregiver and Teacher Report		
	Externalizing	Internalizing	Total	Externalizing	Internalizing	Total	Externalizing	Internalizing	Total
Final outcome variables									
Drug⟶7-y CBCL	0.21	NS	0.16	NS	NS	0.11	0.34	NS	0.16
Drug⟶3-y CBCL	NS	0.11	NS	0.14	NS	NS	0.12	NS	0.11
Drug⟶7-y SES	−0.20	−0.21	−0.20	−0.22	−0.20	−0.20	−0.21	−0.21	−0.21
7-y SES⟶7-y CBCL	−0.09	−0.07	−0.10	−0.14	−0.16	−0.14	−0.16	−0.23	−0.16
Drug⟶NNNS	0.16	0.15	0.16	0.16	0.16	0.16	0.16	0.16	0.16
NNNS⟶IBQ	0.21	0.17	0.22	0.20	0.18	0.23	0.19	0.19	0.20
IBQ⟶3-y CBCL	0.27	0.25	0.29	0.28	0.27	0.31	0.29	0.27	0.28
Total variance explained in the final outcome variables									
R^2	0.31	0.18	0.32	0.07	0.03	0.22	0.35	0.60	0.52
Goodness-of-fit statistics									
CFI	0.971	0.968	0.972	0.971	0.968	0.975	0.976	0.956	0.975
TLI	0.963	0.959	0.963	0.962	0.957	0.966	0.971	0.944	0.968
P	.001	.001	.001	.002	.001	.005	.006	.000	.004
χ^2/df	2.04	2.07	2.04	1.94	2.02	1.83	1.73	2.22	1.80
RMSEA	0.035	0.036	0.035	0.033	0.035	0.031	0.030	0.038	0.031

All path coefficients are significant ($P < .05$) unless otherwise indicated as nonsignficant (NS). NS paths were removed from the final models. DF indicates degrees of freedom; RMSEA, root mean square error of approximation.

tested individually for caregiver and teacher reports as well as combined caregiver and teacher reports on the CBCL. Additional models were tested for each CBCL broadband scale. A total of 9 models were examined for this study. In these models, a direct effect exists when 1 latent variable predicts another latent variable, whereas an indirect effect occurs when a third variable meditates the relationship between 2 latent variables. A path coefficient is a measure of the magnitude of the effect between latent variables, and the total variance of a model indicates how much of an effect is attributable to all variables in the model.

RESULTS

Development of Latent Variables

Latent variables were successfully developed for the 9 models. A single latent prenatal exposure variable that included all 4 substances (cocaine, tobacco, alcohol, and marijuana) was developed. On the NNNS, the latent variable was composed of 2 summary scales, including arousal and the number of stress abstinence signs. A positive score indicates infants who were highly aroused and stressed during the examination. The IBQ latent variable was composed of distress to novelty and distress to limits. A positive score describes infants who become upset in novel situations or when limits are set. A latent variable was not necessary for the 3- or 7-year caregiver or teacher CBCL because we developed separate models for the broadband scales; however, a latent variable was developed for the 3 models in which caregiver and teacher CBCL scores were used together. Positive scores indicated that both parents and teachers rated the child as having more externalizing, internalizing, or total behavior problems. The variables that were included in these factors were determined by the results of the exploratory and confirmatory factor analysis. Both factor loadings, the correlation between a variable and a latent variable, and root mean square residuals, a statistic that is used to measure the appropriateness of a model, were adequate for each latent variable. For example, root mean square residuals for the polydrug factor was 0.027, and the factor loadings were .874 for cocaine, .810 for tobacco, .539 for alcohol, and .669 for marijuana.

SEM Findings

Goodness-of-fit results indicated that all 9 models met statistical criteria for an adequate fit (Table 3). For ease of interpretation, Fig 1 is a schematic of the model that uses combined caregiver and teacher report. Latent variables are in circles and observed variables are in squares. Figure 1 shows 4 pathways (bolded) from prenatal drug exposure to behavior problems on the CBCL at 7 years: (1) prenatal substance exposure is related to lower SES ($\beta = -.21$) and, in turn, predicts behavior problems at 7 ($\beta = -.16$); (2) direct effect of prenatal substance exposure on behavior problems at 7 ($\beta = .16$); (3) direct effect of prenatal substance exposure on behavior problems at 3 ($\beta = .11$), which is related to behavior problems at 7 ($\beta = .65$); and (4) infants with prenatal substance exposure show higher arousal and more stress abstinence signs at 1 month on

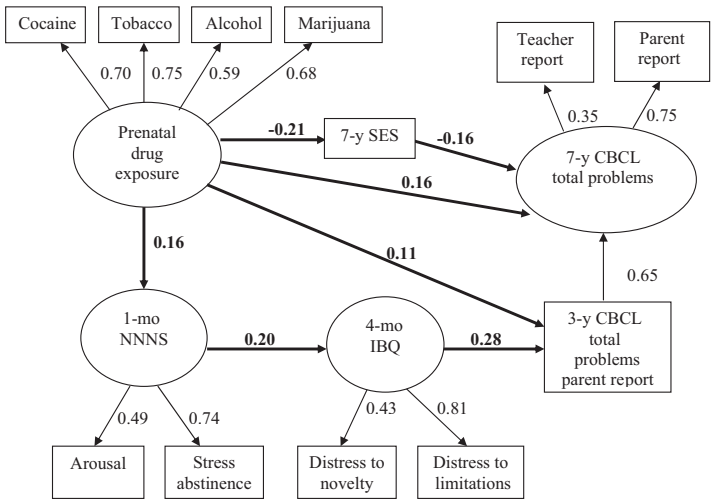

FIGURE 1

Total problems at 7 years by parent and teacher report. CFI = 0.975, TLI = 0.968, RMSEA = 0.031, χ^2/degree of freedom ratio = 1.80. All indicator loadings and path coefficients are significant ($P < .05$).

the NNNS ($\beta = .16$). Temperamentally, these infants showed distress to novelty and limitations at 4 months ($\beta = .20$). These temperamentally difficult infants showed behavior problems on the CBCL at 3 years ($\beta = .28$), which, in turn, predicted behavior problems on the CBCL at 7 years ($\beta = .65$). The entire model explained approximately half (52%) of the variance in total behavior problems at 7 years.

The standardized path coefficients for the models that predict externalizing, internalizing, and total behavior problems all were statistically significant ($P < .05$) unless otherwise indicated (Table 3). Overall, 63 (88%) of the 72 paths were statistically significant, and 7 of the 9 models explained between 18% and 60% of the variance in behavior problems at age 7. This suggests that the relationships among these variables were relatively stable across types of behavior problems (externalizing, internalizing, and total) and reporters (caregiver, teacher, and combined caregiver and teacher). All of the path coefficients along the indirect (developmental) path from prenatal substance exposure to NNNS, IBQ, 3-year CBCL, and 7-year CBCL were statistically significant. All path coefficients that were not statistically significant were direct paths from prenatal drug exposure to the 3- or 7-year CBCL (9 of the 18 possible paths), although the most robust finding was the direct path from substance exposure to caregiver and parent report of externalizing behavior problems at age 7. This may suggest that in these models, the indirect drug effects of prenatal substance exposure are more robust than the direct effects of prenatal substance exposure.

Testing Alternative Models

For all models (Table 3), we examined model fit statistics and parameter coefficients with and without the direct effects of poly substances on 3-year and/or 7-year CBCL outcomes and included only models with the best fit. We tested a number of alternative models, including models with cocaine as the only substance, models with cocaine excluded from the latent drug variable, models for level of prenatal drug exposure (eg, heavy exposure), separate models for boys and girls, models with birth weight as a mediator of drug effects on the CBCL, and models with other measures of the postnatal caregiving environment (eg, quality of the home environment, parenting stress, maternal psychopathology). These alternative models were rejected because there was no convergence, the model fit statistics did not meet criteria (Comparative fit index (CFI) $\geq .95$ and Tucker-Lewis index (TLI) $\geq .95$), or they showed poorer fit statistics.

DISCUSSION

We found evidence of a developmental model suggesting both direct and indirect effects of prenatal exposure to cocaine and other substances on behavior problems in childhood. The indirect effects show a sequence of connected behavioral alterations starting in the neonatal period that lead to later behavior problems. Prenatal substance exposure predicted higher infant reactivity and stress at 1 month, which led to a more difficult temperament at 4 months. In turn, difficult temperament was associated with more behavior problems at 3 and 7 years. These indirect effects of prenatal substance exposure were observed in the presence of the direct effects of prenatal substance exposure and effects of SES on these behavioral outcomes. In other words, the indirect effects remained after controlling for the direct effects of prenatal substance exposure and SES. This suggests multiple pathways, both direct and indirect, from prenatal substance exposure to behavioral outcomes in childhood and that the effects are cumulative.

The direct paths may be thought of as teratogenic effects and support previous findings relating prenatal substance exposure to caregiver report of behavior problems in school-aged children.[5,21,22] Our findings suggest that these may be "true" teratogenic effects because they remained when indirect effects were also included. Conversely, half of the direct path

coefficients failed to reach statistical significance in the SEMs (Table 3), suggesting that these effects are less robust than when tested with more traditional regression analysis. These findings also provide an alternative complementary model for studying unique (direct) effects of prenatal substance exposure. In addition, both direct and indirect effects were found in some models, indicating that they explain additive portions of the variance.

Our finding that SES mediates the effects of prenatal substance exposure on childhood behavioral problems is consistent with previous findings.[23–25] Clearly, this is not a "causal" model; prenatal substance exposure does not "cause" low SES. Rather, SES is a proxy for postnatal environmental factors that are associated with substance use during pregnancy related to childhood behavior problems. Other factors, including quality of the home environment,[26,27] maternal psychopathology,[28] and parenting stress[29] that are associated with the caregiving environment of mothers who used substances during pregnancy, were also examined, but these models did not meet statistical criteria or were weaker than models with SES.

We included teacher and caregiver report of behavior problems. In previous work, prenatal cocaine exposure has been related to behavior problems by using teacher report.[30,31] In contrast, we averaged teacher and caregiver report because the combination of 2 independent reports of behavior in different settings might provide a more complete assessment than either report alone. This may explain the higher total variance explained in the models for the combined caregiver and teacher report than for the separate report models.

Our results demonstrate a logical sequence of cascading effects on developmental processes that lead to behavior problems in children with exposure to cocaine and other substances. This pathway could explain some of the behavioral origins of neurobehavioral disinhibition in later childhood related to adolescent substance use.[9–11] Neurobehavioral disinhibition includes many of the behavioral dimensions that are reminiscent of the behaviors measured in our study, including emotional lability, irritability, difficult temperament in infancy, and externalizing and internalizing behavior problems. In older children, these behaviors are subsumed under the broader categories of dysregulated emotion and behavior undercontrol. Neurobehavioral disinhibition is thought to be attributable to dysfunction of the prefrontal cortex and also includes deficits in executive function that were not measured in this study. We need to continue to follow the children in our study to determine whether this developmental pathway extends to the profile of neurobehavioral disinhibition and later substance use in adolescence. Nonetheless, we demonstrated that some precursors of neurobehavioral disinhibition have behavioral echoes in early infancy.

Study Limitations

The limitation of SEM is that alternative models that fit the data as well as or better than the model developed in this study could be developed. Although we examined alternative models (eg, using measures of the caregiving environment), it is possible that other caregiving environment measures would also result in adequate models. The model that we tested was theoretically based, and we acknowledge that it could be modified. In addition, we did not measure genetic influences that are potentially involved in the development of behavior problems.

Three of the 4 measures of child behavior were based on caregiver or teacher report and could have been strengthened with the addition of more objective measures. The path coefficients between the 3- and 7-year CBCL scores were stronger when caregiver report was used at both ages than when caregiver report was related to teacher report (Table 3), suggesting possible reporter bias. An alternative explanation is that the observations of caregivers and teachers reflect the different contexts in which they interact with the children, supporting the decision to average caregiver and teacher scores.

Prenatal substance exposure was a single factor that was based on the presence or absence of each substance examined, including nicotine, alcohol, marijuana, and cocaine. We tested models that included estimates for each individual substance and the amount of exposure to each substance; however, these models did not have adequate goodness-of-fit statistics. The alternative would have been to use cocaine only and acknowledge the presence of other substances, but we thought that it was more accurate to include all substances in a single model. It is interesting that the path coefficients for the 4 substances in the latent substance factor (Fig 1) are similar in size, suggesting that the contribution of each substance to the factor is similar.

Implications

Early identification and prevention of behavior problems is in line with recent recommendations by the American Academy of Pediatrics[32] and would address an important public health need. Our findings suggest that it is possible to identify at 1 month infants who are on a path leading to behavior problems in childhood. Intervention studies could be developed to deter-

mine whether altering behaviors that are measured by the NNNS (ie, reducing arousal and stress) could prevent the development or reduce the magnitude of later child behavior problems. Our findings are optimistic because although we may not be able to treat the children who show direct effects of prenatal substance exposure on childhood behavior problems, we were able to identify children who left in infancy behavioral tracks that may be amenable to treatment. In the long-term, altering the developmental trajectory of these children could address more severe conduct problems and substance use disorders in adolescence.

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