Prenatal Methamphetamine Exposure and Inhibitory Control among Young School-Age Children

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Objective To examine the association between prenatal methamphetamine exposure and inhibitory control in 66-month-old children followed since birth in the multicenter, longitudinal Infant Development, Environment, and Lifestyle study.

Study design The sample included 137 children with prenatal methamphetamine exposure and 130 comparison children matched for race, birth weight, maternal education, and type of insurance. Inhibitory control, an executive function related to emotional and cognitive control, was assessed using a computerized Stroop-like task developed for young children. Hierarchical linear modeling tested the relationship between the extent of prenatal methamphetamine exposure (heavy, some, or none) and accuracy and reaction time outcomes, adjusting for prenatal exposure to alcohol, tobacco, and marijuana; age; sex; socioeconomic status; caregiver IQ and psychological symptoms; Child Protective Services report of physical or sexual abuse; and site.

Results In adjusted analyses, heavy prenatal methamphetamine exposure was related to reduced accuracy in both the incongruent and mixed conditions on the Stroop-like task. Caregiver psychological symptoms and Child Protective Services report of physical or sexual abuse were associated with reduced accuracy in the incongruent and mixed consitions and in the incongruent conditions, respectively.

Conclusion Heavy prenatal methamphetamine exposure, along with caregiver psychological distress and child maltreatment, are related to subtle deficits in inhibitory control during the early school-age years. *(J Pediatr 2012;161:452-9)*.

Methamphetamine use during pregnancy has increased over the past 20 years, with recent estimates suggesting a 5% prevalence in regions with endemic use.[1] There is a paucity of research on the developmental consequences of prenatal methamphetamine exposure in children. Like cocaine, methamphetamine is a psychostimulant that blocks dopamine, norepinephrine, and serotonin reuptake, leading to increased concentrations of these neurotransmitters in the synaptic cleft.[2] Methamphetamine also enhances the release of these neurotransmitters, inhibits monoamine oxidase, and causes maternal vasoconstrictive and anorectic effects.[3] Prenatal methamphetamine exposure may affect widespread neuroontogenic processes, such as cell production and migration,[4] alter the development of the fetal stress response axis,[5] and perturb oxidative-, mitochondrial-, and glutamate-associated excitotoxic pathways, leading to neuronal damage.[6]

Prenatal methamphetamine exposure has been linked to deficits in fetal growth[7] and to effects on infant arousal-regulation, stress reactivity, and motor control,[8,9] which could possibly increase the risk for later problems in cognitive, psychomotor, and behavioral functioning.[10-12] Prenatal methamphetamine exposure may also be associated with deficits in higher-order executive functions that are considered foundational for academic, psychosocial, and behavioral functioning during later childhood and adolescence.[13,14] Neuroimaging studies of community-derived convenience samples[15-17] have identified alterations in frontal-striatal brain regions thought to be related to specific executive functions such as inhibitory control, working memory, sustained attention, and visual-motor integration.[18] Of these skills, inhibitory control (the ability to resist a first impulse or to stay on task despite distraction[19]) is considered particularly important for the development of social competence[20] and emotional and cognitive control.[21] Inhibitory control deficits have been reported in prospective, longitudinal studies of children exposed prenatally to cocaine.[21-25] Here we report the relationship between prenatal methamphetamine exposure and inhibitory control at age 66 months in children enrolled in a large prospective study of prenatal methamphetamine exposure.

CPS	Child Protective Services
IDEAL	Infant Development, Environment, and Lifestyle
SES	Socioeconomic status

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We hypothesized that prenatal methamphetamine exposure would be associated with poorer inhibitory control, and that children with heavier prenatal exposure would have more pronounced deficits.

Methods

Mothers and their infants were enrolled at birth in the longitudinal Infant Development, Environment, and Lifestyle (IDEAL) study of prenatal methamphetamine exposure, conducted at 5 clinical sites in geographic areas with high documented methamphetamine use: University of California Los Angeles, University of Hawaii, Blank Children's Hospital–Iowa Health, University of Oklahoma, and University of Tulsa. Institutional Review Board approval was obtained at each site and included a federal Certificate of Confidentiality. Detailed recruitment methods have been reported previously.[1,26] Maternal exclusion criteria were age <18 years, opiate use during pregnancy, institutionalization for mental and developmental disabilities or emotional disorders, overt psychosis or a documented history of psychosis, and inability to speak English. Infant exclusion criteria were critical illness (unlikely to survive), multiple birth, major life-threatening congenital anomaly, documented chromosomal abnormality associated with mental or neurologic deficiency, overt infection, and having a sibling previously enrolled in the IDEAL study (**Figure**). Between September 2002 and November 2004, a total of 34 833 women delivering at the above sites were screened, of whom 26 999 were available and 17 961 were eligible for participation. The most common reason for ineligibility was having a non–English-speaking mother. Of the eligible mothers, 3705 consented to participate and 14 256 refused. The 21% rate of consent is consistent with those reported in previous studies of this kind.[1] Sociodemographic and substance use information was collected from maternal interviews, including the Lifestyle Interview and Substance Use Inventory. Meconium samples were collected from all infants and analyzed for drug metabolites by a central laboratory (US Drug Testing Laboratory, Des Plaines, Illinois). Methamphetamine exposure was determined by self-report and/or a positive meconium screen with confirmation by gas chromatography–mass spectroscopy.

For longitudinal follow-up, mothers and their infants with prenatal methamphetamine exposure (n = 204) were matched to unexposed comparison mother–infant pairs who denied methamphetamine use and had a negative meconium screen (n = 208). The 2 groups were matched for maternal race, birth weight category (<1500 g, 1500-2500 g, and >2500 g), private versus public insurance, and education (high school diploma vs no high school disploma). Prenatal exposure to alcohol, tobacco, and marijuana was seen in both groups and was considered a background variable. Follow-up assessments were conducted at age 1, 12, 24, 30, 36, 60, and 66 months.

Measures

Inhibitory Control. Executive function at the 66-month visit was measured using the Hearts and Flowers version of the Dots task from the Directional Stroop Battery for school age children.[27] This task tests both inhibitory control and working memory, but in younger children the task's demand for inhibitory control is thought to exert a stronger effect on performance than the memory demand.[27] Certified examiners masked to exposure status administered the task,[19] which was conducted on a laptop computer with children seated approximately 53 cm from a 19 cm × 30 cm computer screen. During each trial, a red heart or a red flower was presented on the left or right side of the computer screen, and the subject was instructed to press either the left or right green-labeled "shift" key in response to the stimulus, depending on the rule, described in more detail later. The trial sequence of events was as follows: plus sign centered on the computer screen (500 msec), blank screen (500 msec), heart or flower presentation (1500 msec or less if the child responds during the interval), and blank screen for 500 msec. The interstimulus interval was 1500 msec, and the maximum trial duration was 3000 msec. The allowable response time from onset of the stimulus was 2000 msec. There were 3 task conditions—congruent, incongruent, and mixed—administered in sequential blocks of trials. Before the first 2 conditions, the child practiced the rule with 4 trials that were identical to the task except that the stimulus remained on the screen until the button was pressed and the child was given feedback and allowed to self-correct. If a child missed 2 out of the 4 practice trials, then additional practice sets, up to a total of 3, were run automatically.

In the congruent condition (first block, with 12 trials), the child followed the rule "press the button on the same side as the heart." In the more difficult incongruent condition (second block, with 12 trials), the child followed the rule "press the button on the side opposite the flower." In the most challenging mixed condition with randomly intermixed congruent and incongruent trials (third block of 33 trials), the child had to hold 2 rules in mind: "heart means same side, and flower means opposite side." Completion of all 3 conditions of the Hearts and Flowers task was a criteria for enrollment in the study. No corrective feedback was provided to the child during test trials. Performance on the task was assessed by the (1) percentage of correct responses or accuracy, measured by dividing correct responses by correct plus incorrect responses; and (2) reaction time, calculated as the mean for correct responses only. Accuracy is considered a more sensitive measure than speed for young children using the incongruent Hearts and Flowers test,[28] and from preschool through school age to adulthood, accuracy measures tend to fit the following pattern: congruent > incongruent >> mixed.[27]

The task was administered to 303 children (74% of the full sample of 412 participating in the 66-month visit) (**Figure**). Twenty-three participants were excluded because of ≥50% invalid trials on any of the 3 trial blocks of the task. A trial was invalid if the child did not respond within 2000 msec or pressed the response key in ≤200 msec, indicating either non–physiologically possible anticipatory guessing or