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Executive Functioning in Preschool-Age Children Prenatally Exposed to Alcohol, Cocaine, and Marijuana

Julia S. Noland, Lynn T. Singer, Robert E. Arendt, Sonia Minnes, Elizabeth J. Short, and Cynthia F. Bearer

Background: Reports from clinical and experimental (animal) research converge on the suggestion that prenatal exposure to alcohol, cocaine, or marijuana undermines executive functioning (EF) and its neurological underpinnings. However, large, adequately controlled, prospective studies of alcohol and marijuana effects on EF have reported conflicting findings, and there have been no such studies of cocaine exposure.

Methods: EF was investigated in a cohort ($n = 316$) of 4-year-old children the majority of whose mothers had used varying combinations of cocaine, alcohol, and marijuana during pregnancy. With use of postpartum maternal report and biological assay, children were assigned to overlapping prenatal cocaine-exposed, alcohol-exposed, and marijuana-exposed groups and to complementary control groups. The postnatal environmental assessment included measures of maternal intellectual and psychosocial functioning, current drug or alcohol use, and home environment.

Results: The children in the alcohol-exposed group had worse tapping-inhibition performance than children in the non–alcohol-exposed group, and this effect persisted when potential confounding environmental variables, other drug variables, and concurrent verbal intelligence were controlled for.

Conclusions: Prenatal alcohol is predictive of decreased EF in early childhood that could not be attributed to environmental factors. The results are discussed in terms of the age and overall high-risk status of the children.

Key Words: Alcohol, Inhibition, Frontal, Prenatal, Cocaine.

EXECUTIVE FUNCTIONING (EF) abilities allow for goal-directed behavior and resistance to competing responses (Fuster, 1989). There is no consensus on the definition of EF, but included in the abilities competing for acceptance under this rubric are working memory, planning, and inhibitory control. This study compares the performance on EF tasks of preschoolers who had prenatal exposure to cocaine, alcohol, and marijuana with that of children without such exposure. Two features of this investigation, in combination, uniquely position it to address the question of prenatal substance-exposure effects on EF. First, the large sample size, prospective design, and extensive assessment of the caregiving environment allow for control not addressed in many reports of the effects of prenatal cocaine and alcohol exposure on EF. Second, we assessed functioning much earlier in development than most investigations of the effects of prenatal substance exposure on EF.

EF tasks were selected for this study on the basis of clinical evidence, which will be reviewed in more detail, that they rely on the functioning of the frontal-subcortical circuit (Diamond et al., 1997; Welsh et al., 1990). Persistent effects on the frontal-subcortical circuit of human infants have been proposed as one of the possible sequelae of prenatal exposure to cocaine (Mayes, 1999), alcohol (Kaemingk and Paquette, 1999), and marijuana (Fried and Smith, 2001). There is neurological evidence of the frontal-subcortical circuit's vulnerability to prenatal exposure to these substances: cocaine (Frick and Dow-Edwards, 1995; Friedman et al., 1996; Spear, 1995), alcohol (Mihalick et al., 2001; Sowell et al., 2002; Wass et al., 2001), and, less directly, marijuana (Glass et al., 1997).

Researchers have reported EF problems in childhood after prenatal cocaine and alcohol exposure, but many had inadequate control of potential environmental confounds. Espy et al. (1999) compared the performance of clinically recruited cocaine- and polysubstance-exposed toddlers with the performance of nonrisk toddlers on an A-not-B task, a clinically validated assessment of EF (Diamond et al., 1997). They found that the substance-exposed toddlers had lower scores. However, the sample was small, and there was inadequate investigation of potential confounds. The controls were not matched on socioeconomic status (SES) and were older than the cocaine-exposed toddlers. Noland et al.

From Case Western Reserve University, Cleveland, Ohio.

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Reprint requests: Julia S. Noland, PhD, The Triangle Building, Suite 250, 11400 Euclid Avenue, Cleveland, OH 44106; Phone: 216-844-6211; Fax: 216-844-6233; E-mail: jsn4@po.cwru.edu.

Portions of this research previously presented at the annual meeting of the Cognitive Development Society (1999), Chapel Hill, North Carolina and the biennial meeting of the Society for Research and Child Development (2001), Minneapolis, Minnesota.

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(2003) found that with a prospective design and similar SES controls, heavier cocaine exposure predicted lower performance on the A-not-B task in infants. This later study was still limited by small sample size and lack of control of caregiver psychological functioning.

Studies with clinically referred samples report significant negative effects of prenatal alcohol exposure on a wide range of EF tasks, including working memory, verbal fluency, planning, set shifting, and response to feedback (Kodituwakku et al., 1995; Mattson et al., 1999). Not only have EF deficits been shown in clinically referred samples, but these alcohol-related EF deficits are independent of general intelligence (Connor et al., 2000) and seem to be associated with a distinct abnormality of corpus callosum shape (Bookstein et al., 2002). Despite these important teratogenic findings, most previous studies have several limitations, including imprecise quantification of the amount of exposure, very small sample sizes, and inadequate controls for environmental differences, such as maternal intellectual and psychosocial functioning.

Three previous studies of EF after prenatal substance exposure have used prospective designs with adequate control of potential confounders. Streissguth et al. (1989) found that in 7-year-olds, prenatal alcohol exposure had a moderate relationship with EF performance. However, Richardson et al. (2002) found no independent effect of either prenatal alcohol or marijuana exposure on EF. From a large, prospective study in preschoolers, Fried et al. (1997) reported a significant marijuana effect on EF after controlling for prenatal and postnatal covariates. However, Fried and Watkinson (2002) have recently reported that in adolescence, there were no marijuana effects on EF (as measured by WCST performance) in this cohort.

In summary, there have been no large prospective studies of EF in cocaine-exposed children, and there are conflicting findings from large prospective studies of prenatal alcohol and marijuana effects on EF. Where effects of prenatal alcohol and marijuana exposure have been found, the children were tested at younger ages. In this study, we assessed EF in a young (4 years old) cohort of children the majority of whose mothers had used varying combinations of cocaine, alcohol, and marijuana during pregnancy. The EF tasks assessed in this investigation [category fluency, motor planning, and tapping inhibition (TI)] are similar to tasks that have been clinically validated in adults with frontal lobe injury (Golden, 1981; Milner, 1964; and Luria, 1980, respectively).

These three EF tasks are sensitive to the disruption of the dopamine/prefrontal cortical-subcortical system associated with phenylketonuria (PKU) in preschoolers (Diamond et al., 1997; Welsh et al., 1990). Children with PKU cannot metabolize an amino acid, phenylalanine (Phe), which interferes with the production of dopamine, a neurotransmitter on which the frontal-subcortical circuit selectively depends (Diamond et al., 1994). Even children treated early and continuously for PKU have increased levels of Phe. In these children, higher levels of Phe are associated with decreased performance on the EF tasks, including those chosen for this study, but not with impairment of general intellectual functioning (Diamond et al., 1997; Welsh et al., 1990). Although the category-fluency and motor-planning tasks are largely unchanged from the procedure of Welsh et al., the TI task has been modified from the version published by Diamond et al. (the modification is described in more detail in the next section).

The EF tasks were administered to 316 children at the 4-year-old visit as part of an ongoing investigation of the effects of prenatal cocaine exposure. In previous studies of this cohort, prenatal cocaine exposure has been associated with decreased birth weight and head circumference (Singer et al., 2001), increased jitteriness (Singer et al., 2000), decreased receptive language (Singer et al., 1999b), disrupted global mental development (Singer et al., 2002a,b), and behavioral disturbances (Singer et al., 2002b). The postnatal environmental assessment included measures of maternal mental functioning and the home environment. With special attention to the possible confounding effects of these covariates, this study explored the direct and indirect relationships between prenatal substance exposure and EF.

METHODS

Subjects

A total of 316 children participated in the EF test battery. These children and their caregivers are part of a larger prospective study by Singer and colleagues. At birth, 415 mother/infant dyads were recruited equally into two groups: cocaine exposed and cocaine unexposed. The enrollment pool, for exposed and nonexposed groups alike, was composed of mothers without private health insurance who had been targeted for a drug screen by the staff of a large, urban, county-run hospital. Exclusion criteria at the time of enrollment included absence of the meconium test or maternal psychiatric history, primary heroin use, human immunodeficiency virus infection, maternal mental retardation, or serious maternal or infant illness. Of the newborns recruited for the longitudinal study, 405 were living at 4 years of age, of which 376 (93%) were seen at the 4-year visit. The children who were unavailable at 4 years of age were equally likely to be from the cocaine-exposed as the cocaine-nonexposed group (LT Singer, unpublished data, 2003). This protocol was approved by hospital and university review boards, and consent from custodial adults was obtained at birth and at the time of testing. Currently, no information about the diagnosis of fetal alcohol syndrome or fetal alcohol effects was available for this report.

Of the children seen at 4 years of age, 316 (84%) participated in at least one of the EF tests. Administrative reasons for nonparticipation in any EF task were as follows: a home visit was conducted, and a truncated assessment battery was required ($n = 4$); the visit occurred while EF tasks were still in the piloting stage ($n = 2$); or the visit occurred on a day on which no examiner trained in the EF tasks was available ($n = 9$). Other reasons for not participating in the EF tasks were child related: refusal of all EF tasks ($n = 18$), failure of all three EF competency tasks ($n = 3$), or estimated IQ less than 45 ($n = 3$). An additional 21 families had to leave before any of the EF tasks could be administered and were not available for follow-up.

Motor-planning data from 280 children were obtained; an additional 25 failed the competency task, and 25 refused to participate. Category-fluency data were obtained from 259 children; an additional 35 children

failed the competency task, and 37 refused to participate. There were 178 participants in the TI task; an additional 30 children failed the competency task, and 17 refused to participate.

Administration of the TI task was discontinued for 6 months, during which time 103 children participated in the other EF tasks but were exempted from the TI task. Testing was stopped when it was noted that only 31 of the first 144 children qualified for participation in the test trials according to the Diamond et al. (1997) procedure. This hiatus was lifted with the development of a plan to score performance during the training trials as well. Of the variables listed in Tables 3 and 4, the 103 exempted children differed from the other EF participants in that they were less likely to have been exposed to cocaine in utero [$\chi^2(1, n = 316) = 3.84$; $p < 0.05$], were less severely cocaine exposed [unpaired $t(308) = 2.01$; $p < 0.05$], and had caregivers who currently used less cocaine [unpaired $t(194) = 2.01$; $p < 0.05$]. Further, the exempted children tended to more frequently have non-Caucasian birth mothers [$\chi^2(1, n = 316) = 3.84$; $p < 0.05$], smaller head circumferences at birth [unpaired $t(311) = 1.76$; $p < 0.07$], and rearing environments that received less favorable scores on the Home Observation for Measurement of the Environment (HOME) interview [unpaired $t(228) = -2.45$; $p < 0.02$]. However, because potential confounders and mediators are selected on the basis of their significance within the subgroup of children participating in each task, intratask comparisons are not affected. Yet the differences between the whole group and the TI-participating subgroup could limit the appropriateness of between-task comparisons. To investigate this potential limitation, a secondary analysis was conducted wherein the category fluency and motor planning × exposure group comparisons were conducted within the TI-participating subgroup.

Substance-Exposure Assessment

All biological samples were taken during the birth hospital stay, and the postpartum interview was conducted at the first follow-up interview (approximately 2 weeks postpartum). Assignment into the cocaine-negative exposure group or the marijuana-negative exposure group was based on negative maternal self-report, negative meconium, and negative infant/maternal urine reports. Meconium is the first bowel movement of the newborn. Assignment into the alcohol-negative group was based on negative maternal self-report and negative meconium analysis. Assignments were made by using all available reports but did not require a complete set of reports.

In addition to cocaine metabolites and cannabinoids, the maternal and fetal urine samples were screened for opiates, 0cyclidine, and amphetamines. The initial urine screen used the Syva Emit technique (Syva Co., Palo Alto, CA). If samples were positive, they were sent for confirmation by gas chromatography with specificity for benzoylecgonine (BZE) of 99% at a concentration of 0.3 mg/ml. Meconium was collected from multiple diapers, stirred for homogeneity, screened, and then analyzed with gas chromatography-mass spectrometry. The cutoff limits for the concentrations of the drugs of interest were 25 ng/g for cocaine and metabolites (BZE, meta-hydroxybenzoylecgonine, and cocaethylene), phencyclidine, opiates, and tetrahydrocannabinol and 100 ng/g for amphetamines. Confirmatory electron-impact, selected ion-monitoring gas chromatography-mass spectrometry assays were conducted. Meconium was tested for alcohol exposure through analysis of fatty acid ethyl esters (FAEE), which are a by-product of the metabolism of ethanol and are increased by alcohol consumption (Bearer et al., 1999). The distribution of FAEE in non–alcohol-exposed meconium was established in a Muslim community in Jordan, where there are strong religious and cultural prohibitions against female use of alcohol. The mean level of FAEE in the Jordan control group was significantly less than that of the self-reported alcohol abstainers from our sample (CF Bearer, unpublished data, 2003). If any of the three markers of FAEE was significantly outside the range of the Jordan sample, then the child was classified as alcohol exposed.

Self-report of drug use was investigated with the Maternal Post-Partum Questionnaire (Streissguth et al., 1983) as adapted by Singer et al. (1999a). The frequency estimate (reflecting days per week) was multiplied by the daily amount (reported in terms of marijuana joints, cigarettes, drinks equivalent to 0.5 oz of absolute alcohol, or "rocks" of cocaine) to compute an estimate of use for each time period: the month before pregnancy and during each trimester of pregnancy. These severity scores for the four time periods were then averaged into a single severity score for each substance.

EF Assessment

The 4-year-old visit was conducted in a single 3- to 4-hr session at the hospital-affiliated free-standing laboratory. Child testers were unaware of the substance-exposure status of the children. The EF tests were given toward the end of the testing sessions, after general intelligence [Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R); Wechsler, 1989], language, and emotional-functioning assessments. For each EF task, a competency assessment was devised to determine eligibility for participation in the task itself.

Tapping Inhibition. This task is an adaptation of a test of frontal lobe functioning developed and validated by Luria (1980) which was adapted by Diamond and Taylor (1996) for use with children 3.5 through 7 years of age. Using this procedure, Diamond et al. (1997) found differential performance of 15 PKU children and 15 matched control children. In this task, a child must tap once if the tester models a double tap and twice if the tester models a single tap. After demonstrating that they had mastered the opposition rules, children attempted to respond appropriately on a block of 16 test trials. If they could not demonstrate mastery of the rules in the pretest, then in accord with Diamond and Taylor (1996), testing was discontinued. Because less than 30% of our initial participants made it to the test trials, we decided to quantify performance in the training and test trials according to the formula described in Table 1. This system was based on face value weightings of the various training and test trial performance points as they accord to the PKU-related performance differences (Diamond et al., 1997). Diamond et al. (1997) reported that the ease of learning the tapping rules was sensitive to differences between children with PKU and controls. In response to a reviewer's concern, we note that this was the only alternative scheme ever applied to the data.

There is precedence for combining learning and test trials in a similar adaptation of the three-pegs test, on which children with PKU were impaired (Diamond et al., 1997). As further support for this adaptation, Schneider et al. (2001b) found that prenatal alcohol exposure in nonhuman primates leads to difficulty in the early learning phase, when contingencies first shift away from a prepotent choice of object. The competency assessment for the modified TI task was three questions from the WPPSI-R reflecting comprehension of the numerical concepts of one and two. If a child failed all three questions, the TI task was not administered.

To begin the task, the experimenter introduced the 1 = 2 rule (I tap once, you tap twice) and presented a single tap. If the child responded correctly, the experimenter went on to the second rule. If the child

Table 1. Formula for Computing Tapping-Inhibition Task Performance

Variable	No. Points
Starting level of points	2
Introduction of 1 = 2 rule.	
Follows rule, no support	3
Follows rule, one support	2
Follows rule, two supports	1
Introduction of 2 = 1 rule.	
Follows rule, no support	3
Follows rule, one support	2
Follows rule, two supports	1
Traditional pretest	
Correct on rule 1 = 2	3
Correct on rule 2 = 1	3
Test phase (only if correct on both pretest trials)	
Correct on >8 of 16 trials	6
Command phase (only if failed pretest)	
Fails "Tap 1 time" command	−1
Fails "Tap 2 times" command	−1

responded incorrectly, learning supports were offered as necessary. The learning supports were (1) enacting the expected numerosity of the response with ink marks and (2) guiding the child's hand to produce the expected response. The experimenter then restated the 1 = 2 rule and offered another chance for the child to demonstrate mastery. Regardless of the child's response, the experimenter introduced the 2 = 1 rule (I tap twice, you tap once) and presented a double tap. If the child's response was correct, then the experimenter moved onto the next phase. If the response was incorrect, then learning supports were offered as necessary, and the experimenter presented another chance to demonstrate competency.

After these training trials, the pretest phase was conducted. At this point, both rules were stated, and then the series of 16 test trials [presented in the order described by Diamond and Taylor (1996)] began and proceeded without any further feedback. As with Diamond and Taylor, if the child failed either of the first two trials, the test trials stopped.

Category Fluency. Phonemic fluency tasks are sensitive to frontal lobe dysfunction (Milner, 1964) but are inappropriate for the prereaders in this study. A subset of the McCarthy Scales of Children's Abilities, adapted for use with children 3 to 12 years of age (Welsh et al., 1991), was truncated and used in this study. The total number of correct, unique exemplars produced across the two categories (food and animals) within the 60-sec time limit was the measure of interest. Welsh et al. (1990) found that PKU children ($n = 11$; mean age, 4.5 years) had significantly lower category fluency than IQ-matched control children and that this effect was independent of SES. The competency task consisted of giving the exemplar "red" and asking for color exemplars; one correct exemplar was needed to proceed to the test phase.

Motor-Planning Task. Finger sequencing is sensitive to frontal lobe injury in adults (Golden, 1981), and Welsh et al. (1991) adapted this task for children. In this motor-planning task, subjects must touch each of their four fingers, in sequence and without repetition, with their same-hand thumb. They were tested first with their dominant and then with their nondominant hand. The number of successful sequences completed in 10 sec on the two hands was summed. Children with PKU ($n = 11$; mean age, 4.5 years) were able to produce fewer sequences than controls, although this effect was only marginally significant (Welsh et al., 1990). The competency task required producing one correct practice sequence.

Verbal, Performance, and Full-Scale IQ. Some previous investigations have reported the effects of prenatal substance exposure on EF and attention abilities that persist after controlling for individual variance in global mental functioning (Espy et al., 1999; Fried et al., 1997; Leech et al., 1999). In this study, performance on six subsets of the WPPSI-R was prorated to produce verbal IQ, performance IQ, and full-scale IQ estimates. Two of the three subtests that constitute the performance IQ estimate have been identified as particularly sensitive to EF ability (Fried et al., 1997). For this reason, the verbal IQ estimate was selected for the discriminate outcome measure, as opposed to the global IQ measures that have been used in previous research (Fried et al., 1997; Leech et al., 1999).

Parental/Environmental Assessment

Not only was drug-use information collected at the postpartum assessment, but we also administered a questionnaire designed to yield a global index of psychiatric symptom severity [Brief Symptom Inventory (BSI); Derogatis, 1992] and an assessment of maternal verbal IQ [Peabody Picture Vocabulary Test—Revised (PPVT-R); Dunn and Dunn, 1981].

At the 4-year-old visit, the preschool version of the HOME (Bradley and Caldwell, 1976) was orally administered to the current caregiver. In addition, the maternal substance-abuse interview was updated, providing data on caregivers' current substance use. The BSI was also updated, and, where there was a new caregiver, a new PPVT-R test was administered.

Methods of Data Analysis

Main effects of binomial substance-exposure grouping variables (exposed/nonexposed) were explored with *t* tests. Statistically significant ($p < 0.05$) effects of substance-exposure groupings were explored with multiple regression analyses. The variables evaluated as potential confounders, mediators, and moderators are listed in Tables 3 and 4. Confounders and mediators are identified the same way statistically (as different by group and related to outcome). However, if an exposure-group effect disappeared with a confounder in the model, then we would conclude that there is no reportable independent substance-exposure effect. In contrast, if the inclusion of a mediator (e.g., gestational age) eliminates the statistical relationship of a substance and an outcome, then the effect of the substance can still be interpreted as acting on the outcome through its effect on the mediator (e.g., cocaine affects EF through its effect on the length of gestation). Moderators are related to outcome variables and aid in interpreting any significant effects.

The following covariates were considered as potential confounders if they were both differentiated ($p < 0.10$) by target exposure grouping and related ($p < 0.10$) to the outcome variables of interest: race, gender, birth mother characteristics (age, education, PPVT-R, block design, picture completion, SES, BSI, and marital status), and current caregiver characteristics (education, PPVT-R score, block design and picture completion, SES, BSI, marital status, and HOME interview). Other gestational drug exposure and current maternal drug use were entered regardless of their relation to the outcome variables or target substance. The following variables were considered potential mediators if they both differentiated ($p < 0.10$) target exposure groupings and were related ($p < 0.10$) to the outcome variables of interest: gestational age (from hospital records); birth length, weight, and head circumference; and number of prenatal visits. Current child verbal IQ was considered a possible moderator. The order in which variables were entered into the regressions followed precedence established in previous work with this cohort (Singer et al., 2000, 2001, 2002a). For the initial regression analysis, potential confounders were followed by the severity scores for nontarget substances, with the target substance grouping binomial entered last. For the final model, potential mediators and moderators were entered after substance-exposure variables. Relationships between maternal reports of exposure severity and the EF measures were explored with Spearman correlational analyses.

Secondary Analysis

It has been proposed that the cognitive effects of prenatal alcohol (Jacobson et al., 1998), marijuana (Fried and Watkinson, 1990), and cocaine (Singer et al., 2000, 2001) may not be apparent at less than a given threshold of exposure. The analyses were rerun comparing a combined no- or lower-use group with a heavier-use group according to previously reported thresholds. For alcohol, those mothers reporting an average severity score greater than seven standard drinks per week were classified as heavier users, according to the criteria of Jacobson et al. (1998). For marijuana, mothers reporting an average use greater than five joints per week were classified as heavier users according to Fried and Watkinson (1990). For cocaine users, classifications previously assigned for this cohort were used. The classifications are based on meconium screen or self-report indicating cocaine metabolites or self-reported severity of use above the 70th percentile (Singer et al., 2001).

RESULTS

Tobacco and alcohol were used during pregnancy by most of the biological mothers (72 and 66%, respectively); cocaine was used by 48% of the mothers and marijuana by 29%. Most biological mothers were minority race (88%), unmarried (88%), and lower SES (98%). The group means for biological mother verbal IQ scores (PPVT-R score: mean, 75.1; SD, 15) were significantly below average. At the time of the 4-year visit, 65 (21%) of the children were living in foster care, were living with biological relatives other than their mothers, or had been adopted.

TI performance was significantly lower in the alcohol-exposed group, and maternal report of the severity of alcohol use during pregnancy was associated with poorer TI performance (Table 2). TI performance was not different between cocaine and marijuana groups and their controls, nor was it related to severity of exposure to these substances. Motor-planning and category-fluency task performances were the same across all substance-exposure groupings and were unrelated to severity scores.

Of the 173 children for whom there were TI data and an alcohol-exposure status classification (unexposed, $n = 60$; exposed, $n = 113$), most participated in both the category-fluency task (unexposed, $n = 49$; exposed, $n = 97$) and the motor-planning task (unexposed, $n = 51$; exposed, 91). When analysis included just these 173 children, all of the main effects were the same. There were still no differences in the performance of the alcohol-exposed and -unexposed groups on the category-fluency task [unpaired $t(2,140) = -0.32$; $p < 0.75$] or the motor-planning task [unpaired $t(2,80) = 0.36$; $p < 0.75$], nor were the marijuana-exposed and -unexposed groups different on the fluency [$n = 142$; $t(140) = 0.71$; $p < 0.48$] or motor-planning [$n = 146$; $t(144) = -0.4$; $p < 0.69$] tasks. Likewise, there was no difference between cocaine-exposed and -nonexposed groups on the fluency [$n = 142$; $t(140) = 0.65$; $p < 0.37$] or motor-planning [$n = 146$; $t(144) = -0.21$; $p < 0.83$] tasks.

To explore the unique variance predicted by gestational alcohol exposure on TI performance, we sought to identify ($p < 0.10$) potentially confounding and mediating variables (Tables 3 and 4). These comparisons were made on the 173 infants who participated in the TI task. As can be seen in Table 3, within this subset of participants, the birth mothers of the alcohol-exposed children were older and tended to be more likely to have taken benzodiazepines during gestation. The birth mothers of the alcohol-exposed children reported using more cocaine, tobacco, and marijuana during pregnancy than did the mothers of nonexposed children. The birth mothers of the alcohol-exposed group reported more symptoms of psychological distress at the time of their children's birth on the BSI.

According to the HOME interview (Table 3), the current caregivers of the alcohol-exposed children reported a home environment less supportive of cognitive development. Additionally, the current caregivers of the alcohol-exposed children reported having used more marijuana and alcohol in the prior 2 years than the caregivers of the unexposed children. Boys and girls were evenly distributed between the alcohol-exposed and alcohol-unexposed groups [$\chi^2(1, n = 173) = 1.5$; $p < 0.22$]. As can be seen in Table 4, the alcohol-exposed children were smaller on all birth measures. At 4 years of age, the alcohol-exposed children tended to have lower full-scale, verbal, and performance IQ scores on the WPPSI-R.

We explored the relationship between TI performance and the previously mentioned covariates to identify potential confounders and mediators. Of these, only maternal age and the child's concurrent IQ scores were significantly related to TI performance (Table 5).

In model 1, the alcohol-exposure grouping was a significant predictor of TI performance, even when maternal age was included in the model (Table 6). Model 2 included maternal age; severity of gestational cocaine, tobacco, and marijuana exposure; and current caregiver use of substances (Table 7). The alcohol-exposure grouping variable remained a significant predictor of TI. Model 2 was repeated without the nine children whose mothers reported benzodiazepine (diazepam) use during pregnancy. The gestational alcohol exposure remained a significant predictor of performance [alcohol exposure status: $\beta = -2.4$; SE = 1.0; $p < 0.03$; model $F(8,126) = 1.22$; $R^2 = 0.07$]. In model 3, concurrent verbal IQ was added to maternal age; severity of gestational cocaine, tobacco, and marijuana exposure; and severity of current caregiver substance use. The alcohol-exposure grouping variable was still a significant predictor of TI when verbal IQ was included in the model (Table 8).

As seen in Table 9, there were no statistically significant differences by threshold grouping on any of the EF tasks. In

Table 2. Performance by Exposure Grouping and Correlations With Severity of Substance Exposure

Variable	Exposed			Unexposed					
	n	Mean	SD	*n*	Mean	SD	*t*	*df*	*r*[a]
Alcohol									
Tapping inhibition	114	7.7	5.4	59	9.7	5.9	2.34*	171	−0.17*
Category fluency	171	4.4	2.9	83	5.1	3.3	−0.2	251	0.01
Motor planning	185	3.4	1.9	90	3.3	2.2	−0.5	273	0.01
Cocaine									
Tapping inhibition	92	7.9	5.7	86	9	5.6	1.25	173	−0.09
Category fluency	128	5.0	3.4	131	5.4	3.3	0.9	254	−0.03
Motor planning	134	3.5	2	146	3.3	2	−0.7	275	0.06
Marijuana									
Tapping inhibition	53	8.4	6	116	8.2	5.4	−0.2	165	−0.01
Category fluency	74	5.3	3.2	175	5.2	3.4	−0.3	246	0.04
Motor planning	76	3.5	2	194	3.3	2	−0.8	266	0.01

[a] Spearman correlations, maternal report.
* $p < 0.05$.

Table 3. Characteristics of Mothers/Caregivers of Participants in Tapping Inhibition Task, by Alcohol-Exposure Grouping

Variable	Alcohol-exposed			Non–alcohol-exposed					
	n (%)	Mean	SD	*n* (%)	Mean	SD	*df*	t/χ^2	*p* Value
Gestational drug use									
Tobacco, severity[a]	112	10.6	11.8	59	5.6	8.2	113	−3.9	0.0001
Alcohol, severity[b]	113	10.6	18.5	58	—	—			
Marijuana, severity[c]	107	1.5	4.3	58	0.3	1.2	163	−2.8	0.01
Cocaine, severity[d]	112	13.6	28.3	58	11	51.6	168	−3.7	0.001
Amphetamine use	5 (2%)			1 (1%)			1	0.01	1
Barbiturate use	2 (2%)			0 (0%)			1	1	0.54
Benzodiazepine use	9 (11%)			0 (0%)			1	4.5	0.06
Heroin use	1 (1%)			0 (0%)			1	0.6	1
Phencyclidine use	4 (4%)			0 (0%)			1	2.1	0.3
Birth mother characteristics									
Race (non-Caucasian)	96 (85%)			50 (83%)			1	0.1	0.78
Married	10 (9%)			10 (17%)			1	2.3	0.14
Lower SES	112 (99%)			58 (97%)			1	1.4	0.28
Age (years)	113	28	5.1	60	26.2	5.5	171	2.2	0.03
Years of education	113	11.7	1.6	60	11.9	1.5	171	0.9	0.39
Parity	113	2.9	1.8	60	2.9	1.6	171	−0.23	0.82
Gravida	113	4.3	2.2	60	4	2.2	171	−0.92	0.36
No. prenatal visits	113	6.4	4.8	60	6.7	4.9	171	0.42	0.67
PPVT_R score	112	74.6	14.1	60	77.2	14.6	170	1.1	0.27
WAIS-R block design	111	7.2	2.2	60	6.9	2.2	169	−0.73	0.46
WAIS-R picture completion	111	6.8	2.3	60	7.2	2.3	169	−1.2	0.23
BSI	113	0.66	0.68	56	0.51	0.52	148	−2.1	0.04
Current caregiver									
Current alcohol, severity	99	4.3	14	53	1.3	3.8	148	−2.64	0.01
Current marijuana, severity	98	0.6	4.1	53	0	0	142	−2.4	0.02
Current cocaine, severity	99	8.8	59.4	53	0.07	0.5	97	−1.6	0.12
HOME score	113	40.6	6.4	60	42.6	7.2	116	1.94	0.05
PPVT_R score	106	79.2	15.9	56	78.3	14.8	171	−0.35	0.73
WAIS-R block design	105	7	2.2	55	7.3	2.3	160	0.73	0.47
WAIS-R picture completion	105	7.1	2.4	55	6.7	2.3	158	1	0.32
BSI	96	0.46	0.53	53	0.36	0.44	147	−1.1	0.26

WAIS, Wechsler Adult Intelligence Scale, Revised.
[a] Mean number of cigarettes/day.
[b] Mean number of drinks/day × number days/week.
[c] Mean number of joints/day × number days/week.
[d] Mean number of "rocks"/day × number days/week.

Table 4. Characteristics of Tapping Inhibition Task Participants, by Alcohol-Exposure Group

Variable	Alcohol-exposed (n = 113)		Non–alcohol-exposed (n = 60)				
	Mean	SD	Mean	SD	*df*	χ^2/F	*p* Value
Birth Characteristics							
Gestational age (weeks)	38.3	2.4	38.4	2.2	171	<0.1	0.93
Birth weight (kg)[a]	2.87	0.04 (SE)	3.15	0.06 (SE)	1	14.9	0.001
Birth length (cm)[a]	48.3	0.23 (SE)	49.1	0.32 (SE)	1	3.9	0.05
Head circumference (cm)	33	0.14 (SE)	33.8	0.19 (SE)	1	11	0.01
Intellectual functioning							
WPPSI-R full-scale IQ	83.9	12.4	87.4	11.8	171	1.8	0.08
WPPSI-R verbal IQ	82.7	11.2	85.6	11.1	171	1.7	0.1
WPPSI-R performance IQ	88.4	14.0	92.1	14	171	1.7	0.1

[a] Variance in birth size associated with gestational age controlled for statistically.

another follow-up analysis, the relationship of prenatal alcohol-exposure status and TI performance was explored for the subgroup of subjects who had had no gestational cocaine exposure. In this subgroup, as with the whole group, prenatally alcohol-exposed infants (n = 40; mean, 7.8; SD, 5) had lower scores than alcohol-unexposed infants (n = 44; mean, 10; SD, 5.8), although this difference was only marginally significant [$t(82) = 1.86$; $p < 0.07$]. There were no covariates that qualified ($p < 0.10$) as potential confounders or mediators of this relationship. However, prenatal alcohol-exposure status was not a significant predictor of TI performance when the severity of current caregiver marijuana and alcohol use were added to the regression model [alcohol exposure status: $\beta = -1.6$; SE = 1.3; $p < 0.22$; model $F(3,71) = 1.03$; $R^2 = 0.04$]. Germane to understanding this relationship is a comparison indicating that significantly more [$\chi^2(1, n = 173) = 29.4$; $p < 0.001$] of the cocaine-exposed children (37%) had been placed out of the biological mother's care, whereas only 4% of the non–cocaine-exposed children had. The lower rates of

Table 5. Continuous Relationship of Tapping-Inhibition Performance With Drug Severity Variables and Variables Differing ($p < 0.10$) Between Alcohol-Exposure Groups

Variable	Relations with TI	*p* Value
Biological mother		
Tobacco severity, prenatal	0.07[a]	0.32
Age[b]	−0.13[c]	0.08
BSI: Global Severity Index[b]	−0.03[c]	0.7
Benzodiazepines, any use, prenatal	1.13[d]	0.26
Current caregiver		
HOME interview	0.1[c]	0.19
Current alcohol, severity	0.06[a]	0.47
Current marijuana, severity	−0.02[a]	0.81
Current cocaine, severity	−0.03[a]	0.7
Birth outcomes[e]		
Weight	<0.01 (<0.01)[e]	0.93
Length	0.04 (0.17)[f]	0.83
Head circumference	0.25 (0.29)[f]	0.37
Intellectual functioning (child)		
Full-scale IQ	0.27[c]	0.001
Verbal IQ	0.3[c]	0.0001
Performance IQ	0.2[c]	0.01

[a] Spearman *r*.
[b] Assessed at the time of child's birth.
[c] Pearson product-moment correlation, *r*.
[d] *t* test.
[e] Analysis adjusted for gestational age.
[f] Multiple regression analysis, β, SE.

Table 6. Effects of Prenatal Alcohol Exposure on Tapping Inhibition: Model 1, Including Potential Environmental Confounders, but Not Potential Drug Confounders

Predictor	β (SE)	*t*	*p* Value
Maternal age	−0.11 (0.08)	−1.4	0.16
Prenatal alcohol-exposure status	−1.96 (0.9)	−2.2	0.03

$F(170,2) = 3.9$; $p < 0.02$; $R^2 = 0.05$.

Table 7. Effects of Prenatal Alcohol Exposure on Tapping Inhibition: Model 2, Including Potential Drug Confounders

Predictor	β (SE)	*t*	*p* Value
Maternal age	−0.01 (0.09)	−0.15	0.88
Current cocaine use, severity	−0.34 (0.6)	−0.58	0.56
Current alcohol use, severity	0.56 (0.48)	1.18	0.24
Current marijuana use, severity	−0.39 (1.31)	−0.3	0.76
Gestational marijuana use, severity	0.16 (0.78)	0.2	0.84
Gestational tobacco, severity	0.23 (0.43)	0.54	0.59
Gestational cocaine, severity	0.02 (0.36)	0.08	0.93
Prenatal alcohol exposure, status	−2.47 (1.0)	−2.38	0.02

$F(134,8) = 0.93$; $p < 0.5$; $R^2 = 0.05$.

out-of-home placements and the resultant increase in pre- and postnatal concordance may have made requiring an effect of prenatal exposure that was independent of postnatal caregiver substance use prohibitively conservative.

The performance of the alcohol-exposed (but not cocaine-exposed) group was also compared with the performance of children exposed to both alcohol and cocaine. The addition of cocaine produced no group differences in performance on the TI task [alcohol exposed, $n = 40$; alcohol and cocaine exposed, $n = 73$; $t(111) = 0.27$; $p < 0.79$], category-fluency task [alcohol exposed, $n = 66$; alcohol and cocaine exposed, $n = 104$; $t(168) = -0.0.15$; $p < 0.88$], or motor-planning task [alcohol exposed, $n = 75$; alcohol and cocaine exposed, $n = 109$; $t(182) = 0.11$; $p < 0.91$].

Table 8. Effects of Prenatal Alcohol Exposure on Tapping Inhibition: Model 3, Including Potential Confounders and Verbal IQ

Predictor	β (SE)	*t*	*p* Value
Maternal age	−0.05 (0.09)	−0.23	0.59
Current cocaine use, severity	−0.25 (0.58)	−0.43	0.56
Current alcohol use, severity	0.61 (0.46)	1.31	0.24
Current marijuana use, severity	−0.04 (1.27)	−0.03	0.76
Gestational marijuana use, severity	0.22 (0.75)	0.29	0.84
Gestational tobacco, severity	0.33 (0.42)	0.77	0.59
Gestational cocaine, severity	<0.01 (0.35)	−0.02	0.93
Concurrent verbal IQ	0.13 (0.04)	3.06	0.003
Prenatal alcohol-exposure status	−2.17 (1.0)	−2.16	0.02

$F(133,9) = 1.92$; $p < 0.054$; $R^2 = 0.11$.

DISCUSSION

The relationship of prenatal alcohol exposure status and TI remained significant after controlling for prenatal drug exposures, postnatal environmental factors, and verbal IQ. To explore the generalizability of this effect, we repeated this analysis of the relationship between alcohol exposure and TI, this time excluding children in the cocaine-exposed group. There continued to be worse TI performance from the prenatal alcohol-exposed group, although it reached only the level of a statistical trend. This trend was confounded with one type of environmental measure (current amount of alcohol or marijuana use by caregiver), but was not confounded with other environmental measures (the HOME and caregiver psychiatric/cognitive functioning assessments). This suggests that the negative relationship of prenatal alcohol exposure to TI applies to the cocaine-unexposed children. In support of this suggestion, the alcohol- and cocaine-exposed group was not different from the alcohol-exposed and cocaine-unexposed group on any of the EF tasks.

The TI task requires producing a response that is the opposite of the prepotent response. Several nonhuman primate models of response conflict have been developed (Dias et al., 1996) and provide evidence at the neural level that the frontal cortex is critical for success in response to conflict situations. Controlling behavior when a response bias is in conflict with a correct response is difficult for young children (Diamond, 1990; Roberts and Pennington, 1996). There is a gradual development of success in situations of response conflict over the preschool years [for a review, see Zelazo et al. (1996)]. Studies of experimental frontal lobe damage in young nonhuman primates have allowed us to attribute, at least partially, increasing inhibitory control to development in the frontal-subcortical circuit [for a review, see Goldman-Rakic (1987)].

In the context of previous clinical and experimental studies, this finding can be interpreted as suggesting a direct and persistent effect of alcohol exposure on the frontal-subcortical circuit. With a previous version of the tapping task, Diamond et al. (1997) found that children with dis-

Table 9. Performance on Executive Functioning Tasks by Threshold of Exposure Grouping

Variable	Heavier exposure			Light or no exposure			Kruskal-Wallis test statistic
	n	Mean	SD	*n*	Mean	SD	
Alcohol							
Tapping inhibition	36	7.4	5.5	142	8.7	5.7	1.7
Category fluency	46	4.8	3.4	213	5.3	3.3	1.0
Motor planning	50	3.3	1.8	230	3.4	2.0	0.4
Cocaine							
Tapping inhibition	50	7.8	5.9	128	8.7	5.6	1.7
Category fluency	74	5.0	3.5	185	5.3	3.3	0.8
Motor planning	69	3.6	2.0	211	3.4	2.0	0.5
Marijuana							
Tapping inhibition	9	5.8	3.8	169	8.6	5.7	2.6*
Category fluency	11	5.5	3.8	248	5.2	3.4	0.03
Motor planning	7	3.4	1.8	253	3.4	2	0.1

* $p < 0.10$.

ruptions of prefrontal cortical functioning had difficulty compared with IQ-matched controls. Inhibitory control deficits and perseverations are also reported in animal models of prenatal alcohol exposure [see Driscoll et al. (1990) for a review]. Recently, Mihalick et al. (2001) found that prenatal alcohol–exposed rats have difficulty overcoming prepotent response biases and that this difficulty corresponds to decreased cells in the prefrontal cortex of exposed animals. Similarly, children with clinically diagnosed fetal alcohol syndrome or fetal alcohol effects have difficulty producing a response that is in conflict with a recently acquired (Coles et al., 1997; Kodituwakku et al., 2001) or a long-standing (Mattson et al., 1999) response bias.

Previously, the study of Streissguth et al. (1989) was the one investigation with a large prospectively recruited sample of alcohol-exposed children that reported EF deficits that persisted after controlling for variance in caregiver functioning. Richardson et al. (2002), in a cohort of similar size and low SES, found no effect of prenatal alcohol exposure on the EF. Our results replicate the Streissguth et al. (1989) finding at a significantly younger age (4 years as compared with 7 years).

In this study, there were no relationships of prenatal cocaine exposure or marijuana exposure to TI performance. However, the evidence from infancy suggests that cocaine exposure may negatively affect performance in a response conflict task (Espy et al., 1999; Noland, 2003) and that prenatal marijuana exposure may affect preschoolers' performance in a domain of EF associated with inhibitory control (Fried and Smith, 2001). It is possible that cocaine and marijuana have neuroteratologic effects on the same functional systems as alcohol, but that these effects may be more subtle, may appear earlier in development, or may act at a higher threshold than assessed in this investigation.

No significant effects for any substance exposure were detected on the other two tasks (category fluency or motor planning). However, it would also be a mistake to assume at this point that substance exposures do not affect category-fluency or motor-planning processes. These abilities or processes may not be developed enough at 4 years of age to produce a range of performance sufficient to detect group differences. The frontal lobes have an extended developmental course (Huttenlocher, 1979) and functionally distinct subsystems developing at different rates (Goldman-Rakic, 1987). Welsh et al. (1991) found that the category-fluency and motor-planning tasks loaded on a common developmental factor requiring "speeded and organized responding." If prenatal alcohol, cocaine, or marijuana exposure has a negative effect on speeded and organized responding, it may not be apparent until this subsystem develops more fully.

One possible limit to the generalizability of our finding may be the atypical levels of gestational stress associated with the poverty and psychological distress that was prevalent in the biological mothers in this sample. In animal models, gestational stress has been demonstrated to increase the effects of prenatal alcohol exposure on offspring behavior (Schneider et al., 2001a). However, because a similar alcohol/EF relationship was found in the Streissguth sample (Streissguth et al., 1989) of middle-class social drinkers, the findings of the two studies can be considered together to suggest a more general effect.

EF tests are generally sensitive to developmental disabilities (Pennington, 1991) and, as such, have been recommended for exploratory evaluations of neurotoxic exposure in pediatric populations (Krasnegor et al., 1994). However, beyond increasing the sensitivity of a test battery, EF tasks have the potential to identify particular cognitive domains that should be targeted for intervention. Our finding reinforces the suggestion of Connor et al. (2000), that a history of prenatal alcohol exposure may predict difficulty in flexibly adapting and changing behavior in the face of novelty or new rules.

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