Published in final edited form as:

Neurotoxicol Teratol. 2010 ; 32(6): 580–588. doi:10.1016/j.ntt.2010.06.004.

Effects of Prenatal Tobacco, Alcohol and Marijuana Exposure on Processing Speed, Visual-Motor Coordination, and Interhemispheric Transfer

Jennifer A. Willford^a, Lynette S. Chandler^b, Lidush Goldschmidt^c, and Nancy L. Day^a

^aDepartment of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

^bUniversity of Puget Sound and Department of Occupational Therapy, University of Pittsburgh, Pittsburgh, PA 15213, USA

^cWestern Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, PA, 15213, USA

Abstract

Deficits in motor control are often reported in children with prenatal alcohol exposure (PAE). Less is known about the effects of prenatal tobacco exposure (PTE) and prenatal marijuana exposure (PME) on motor coordination, and previous studies have not considered whether PTE, PAE, and PME interact to affect motor control. This study investigated the effects of PTE, PAE, and PME as well as current drug use on speed of processing, visual-motor coordination, and interhemispheric transfer in 16-year-old adolescents. Data were collected as part of the Maternal Health Practices and Child Development Project. Adolescents (age 16, n=320) participating in a longitudinal study of the effects of prenatal substance exposure on developmental outcomes were evaluated in this study. The computerized Bimanual Coordination Test (BCT) was used to assess each domain of function. Other important variables, such as demographics, home environment, and psychological characteristics of the mother and adolescent were also considered in the analyses. There were significant and independent effects of PTE, PAE, and PME on processing speed and interhemispheric transfer of information. PTE and PME were associated with deficits in visual motor coordination. There were no interactions between PAE, PTE, and PME. Current tobacco use predicted deficits in speed of processing. Current alcohol and marijuana use by the offspring were not associated with any measures of performance on the BCT.

Keywords

Prenatal Alcohol Exposure; Prenatal Tobacco Exposure; Prenatal Marijuana Exposure; Visual Motor Coordination; Speed of Processing; Bimanual Coordination; Motor

© 2010 Elsevier Inc. All rights reserved.

Address Correspondence to: Jennifer Willford, Ph.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, Telephone: 412-681-3482, Fax: 412-681-1261, willford@pitt.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

The Centers for Disease Control and Prevention (CDC, 2002a) estimated that 13% of all children born in the United States were exposed to alcohol during gestation and 10–20% of children were prenatally exposed to tobacco (CDC, 2002a; CDC, 2002b; LeClere and Wilson, 1997; NCI, 1999). The rates of both PAE and PTE are higher among disadvantaged populations (Cornelius et al., 1999; Kahn et al., 2003). Women who drink frequently after pregnancy recognition are more likely to be tobacco users (Floyd et al., 1999), and pregnant women who smoke tobacco are more likely to report drinking during pregnancy (25%) (Ebrahim et al., 2000), and are more likely to be heavy drinkers during pregnancy (USDHHS, 1995). Marijuana use accounts for 75% of illicit drug use during pregnancy and women using marijuana during pregnancy are also more likely to smoke cigarettes and drink (Day et al., 1993; Ebrahim and Gfroerer, 2003).

The global effects of prenatal substance exposure on the developing nervous system appear to be similar, causing alterations in cell adhesion, migration, and cellular communication that disrupt the development of neurotransmitter systems, hormone regulation, growth factors, and intracellular signal transduction (Anthony et al., 2008; Goodlett & Horn, 2001; Levitt, 1998; Malanga & Kosofsky, 1999; Miller, 1993; ¹⁹⁹⁶; Miller & Dow-Edwards, 1988; Miller & Nowakowski, 1991; Miller & Potempa, 1990; Zhou et al., 2003). The underlying neural pathways affected by each substance, however, are different. The primary mechanism for PTE effects on the developing brain is the dysregulation of the timing of trophic events linked to nicotinic cholinergic receptors (nAChRs) (Levin & Slotkin, 1988; Slotkin, 1992; 1998; 1999). PAE affects the development of the nervous system through multiple pathways including action on the cell membrane, glial cell development, hormones, growth factors, and intracellular signal transduction (Druse, 1992; Pennington, 1992; Pentney and Miller, 1992; Ramanathan et al., 1996; West et al., 1994). The primary site of action for PME effects is the endocannabinoid system (Harkany et al., 2007).

Prenatal drug exposure is associated with deficits in multiple cognitive domains. PAE, for example, is associated with deficits in verbal learning and memory, response inhibition, and visual motor integration (Connor et al., 2000; Mattson et al., 1999; Mattson et al., 1998; Richardson et al., 2002; Willford et al., 2004). PTE predicts deficits in visual perception and memory, verbal learning, and auditory functioning (Cornelius et al., 2001; Fried and Watkinson, 2000; Fried et al., 2003). PME is associated with deficits in visual problem solving, sustained attention, and learning and memory (Fried, 2002; Fried and Watkinson, 2000; Richardson et al., 2002). Secondary effects on academic achievement and job performance are also associated with PTE, PAE, and PME (Batstra et al., 2003; Fried et al., 1997; Goldschmidt et al., 2004; Goldschmidt et al., 1996; Howell et al., 2006).

A few studies have reported negative effects of combined alcohol and tobacco exposure on preterm births (Dew et al., 2007), and birth weight, head circumference, and length (Brooke et al., 1989; Haste et al., 1991; Olsen et al., 1991; Shu et al., 1995). No studies have evaluated the interactive effects of PAE and PME on developmental outcomes. The interactive effects of PTE, PAE, and PME on motor function have not been evaluated.

Bimanual coordination tasks measure the efficiency with which information is exchanged between the cerebral hemispheres. Both the motor cortex and corpus callosum (CC) are necessary to perform these tasks. The motor cortex controls movement of the contralateral side of the body. It also controls motor programs that originate in the left hemisphere for skilled movement of the hands and limbs (Kawashima et al., 1993). The CC connects homotopic locations in the two hemispheres of the brain and facilitates interhemispheric communication in order to coordinate movement

There is an association between PAE, CC dysmorphology, and deficits in bimanual coordination. In one study, children with high levels of PAE had variable and inaccurate performance on the bimanual coordination task that was significantly correlated with the overall size as well as with the size of the anterior and posterior regions of the CC (Roebuck et al., 2002; Roebuck-Spencer et al., 2004). Another study found that subjects with PAE had a relatively thin corpus callosum that was associated with deficits in motor function including poor balance, poor motor coordination, more errors, and longer time to correct errors on both a hand steadiness task and a measure of spatial learning (Bookstein et al., 2002).

In addition, PAE predicts deficits in visual motor coordination and fine motor control. Mattson et al. (1998) showed that children with PAE had deficits in their ability to copy difficult geometric patterns, fine motor speed, and eye-hand coordination. Gross motor and fine motor skills were negatively affected by PAE in young children in another study (Barr et al., 1990, Kalberg et al., 2006). At least in one study, however, the childhood deficits in motor control did not persist into adulthood except among those who had higher PAE and additional neuropsychological deficits (Conner et al., 2006). Measures of balance were not affected by PAE (Barr et al., 1990; Chandler et al., 1996).

There is less information on the effects of PTE and PME on motor control. Among infants, PTE was related to poorer overall motor performance (Miller-Loncar et al., 2005) and higher concentrations of cotinine were associated with an increase in the likelihood of hypertonia on neurologic exam (Dempsey et al., 2000). At an older age, PTE predicted significantly slower performance on the Grooved Pegboard task, a measure of eye-hand coordination, in 10-year-olds (Cornelius et al., 2001). No study has found motor control deficits associated with PME (Chandler et al., 1996; Fried and Smith, 2001; Richardson et al., 1995).

Other factors also affect cognitive development. Important factors include maternal cognitive ability, parenting practices, and mother-child interactions (Hall et al., 1991; Landry et al., 2006; Lutenbacher and Hall, 1998; Smith et al., 2006; Tong et al., 2007), child psychopathology (Clark and Kirisci, 1996; Kovacs and Goldston, 1991; Puig-Antich et al., 1985), parental substance use (Collins et al., 2003; Locke and Newcomb, 2004; Moser and Jacob, 1997), and environmental tobacco exposure (DiFranza et al., 2004; Eskenazi and Castorina, 1999; NCI, 1999). The adolescent's substance use is also important as adolescent drug use delays the development of cognitive abilities (Brown et al., 2000; Scheier and Botvin, 1995; Tapert et al., 2002). In 2004, Streissguth and colleagues evaluated the associations between prenatal alcohol exposure, other risk/protective factors, and secondary disabilities. Early diagnosis and stable rearing environments were important environmental variables that served to decrease the likelihood of deficits in adaptive behavior. Thus, it is important to assess these factors when evaluating the effects of prenatal substance exposure on cognitive outcomes.

This study is an evaluation of the effects of prenatal and current tobacco, alcohol, and marijuana exposure on bimanual coordination. The subjects in this study were adolescents who were aged 16 to 18. The hypotheses were that 1) PTE, PAE, and PME will be associated with impairments in unimanual motor speed and visual-motor coordination, 2) Controlling for visual-motor coordination, PTE, PAE, and PME will be associated with deficits in interhemispheric transfer, and 3) The association between prenatal exposures and performance on the bimanual coordination tasks will not be explained by current substance use. The interactions between PTE, PAE, and PME on performance of the bimanual coordination tasks were also explored.

2. Methods

2.1 Participants

The study sample is a subset of subjects who are participants in two cohorts of the Maternal Health Practices and Child Development Project (MHPCD). Women who were at least 18 years of age were approached during their fourth prenatal month clinic visit. Eighty-five percent of the women agreed to participate in the study, resulting in a screening sample of 1360 women. From this sample, two study cohorts were selected based on first trimester alcohol and marijuana use. In the first cohort, women who drank alcohol at least 3 drinks/week, and a random sample of women who drank less often or not at all were selected for a study of the long-term effects of prenatal alcohol exposure. The cut-point of 3 drinks/week was chosen because it was approximately the median value of alcohol use in the original screened population. In the second cohort, women who used marijuana at the rate of 2 or more joints/month and a random sample of women who used marijuana less often or not at all were chosen for the study of the effects of marijuana use during pregnancy. These study cohorts were selected independently and with replacement, so there was overlap in the two samples, resulting in a total sample of 829 women. The two cohorts are combined in these analyses to increase the number of subjects and, therefore, power. This is possible because the two studies are done in parallel with the same instruments, protocols, and personnel. The loss to follow-up was the same in the two cohorts.

Women were assessed at 4 and 7 months of pregnancy and with their offspring at birth and at 8 and 18 months and 3, 6, 10, 14, 16, and 22 (on-going) years of age. At each assessment, women were asked about substance use, life style, current environment, medical history, and demographic status. The children were examined for growth, cognitive, and behavioral development.

By delivery, the combined sample of 829 mothers was reduced to 763 mothers and their live-born singleton newborns. The attrition was due to fetal deaths ($n=18$), adoption ($n=1$), multiple births ($n=2$), moved out of the area ($n=21$), lost to follow-up ($n=16$), and refused further participation ($n=8$). At 16 years, 52 women refused participation, 35 had moved from the Pittsburgh area, 72 were lost to follow-up, 6 children died, and 9 children were adopted or in foster care. As a result, 589 adolescents were assessed. Two hundred sixty-nine subjects did not complete the BCT for the following reasons: Phone assessments were done for 84 adolescents, 8 refused to do the BCT, 4 did not understand the instructions, 81 adolescents were not tested due to time constraints, and 52 tests were not completed due to equipment/computer failure. An additional 37 adolescents did not perform the BCT due to illness, lack of assessor availability, distractions, or unknown reasons, and 3 adolescents were not included due to mental retardation. Therefore, this report is based on the 320 offspring who were assessed with the BCT at the 16-year follow-up.

2.2 Measures

2.2.1 Substance Use—The quantity, frequency, and pattern of use for each substance were assessed at the end of each trimester. For the second and third trimesters, assessment included use across the entire trimester. Prenatal alcohol, tobacco, and marijuana use were used as continuous variables in these data analyses. PAE was expressed as average daily volume (ADV). ADV is a summary measure of the total amount of alcohol consumed, averaged to represent the number of drinks per day by adjusting for the numbers of days/month. PTE was the average number of cigarettes per day, and PME was average daily joints (ADJ). PAE and PME were natural log-transformed to reduce skewness.

2.2.2 Adolescent Characteristics—At age 16, the adolescent's physical and psychosocial characteristics were assessed. Age, race, gender, handedness, and vision problems were recorded as were the number of illnesses, injuries, and hospitalizations since the previous follow-up at age 14. Depression and anxiety were assessed using the Child Depression Inventory (CDI, Kovacs, 1992) and the Revised Child's Manifest Anxiety Scale (RCMAS, Reynolds et al., 1978), respectively. Adolescent alcohol, tobacco, marijuana, and other illicit drug use were measured using the Health Behavior Questionnaire (HBQ, Jessor et al., 1989). Alcohol and marijuana use were defined as the number of drinks or joints per day in the past year, and tobacco use was defined as the number of cigarettes smoked per day in the last thirty days. Illicit drug use in the past year was dichotomized (1 = used, 0 = did not use).

2.2.3 Maternal Characteristics—Depression was assessed during the 16-year follow-up with the Center for Epidemiological Studies-Depression Scale (CES-D; Radloff, 1977). Anxiety and hostility were assessed using the State-Trait Personality Inventory (STPI; Spielberger, 1979). Maternal intellectual ability was estimated with the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale Revised (WAIS-R, Wechsler, 1981) that were administered at the 10-year follow-up. The average estimated maternal IQ was 89 (SD = 10.83) with a range of 61 to 120.

2.2.4 Environmental Characteristics—Current environment was measured using variables that covered multiple domains. Demographic variables included maternal age, work status, marital status, education, and income. The number of children in the household, presence of an adult male in the household, social support, and recent life events were used to evaluate social support and environment. Adolescent perceptions of parental involvement were measured using the acceptance/involvement scale from Steinberg's Parenting Practices questionnaire (Steinberg et al., 1992), which is a self-report measure of the extent to which an adolescent perceives his or her parents to be loving, responsive, and involved. Life events were measured using the Psychiatric Epidemiology Research Interview (PERI) life events scale (Dohrenwend et al., 1978).

2.2.5 Bimanual Coordination Task—A computerized Bimanual Coordination Test (BCT) was used (Brown, 1991). The BCT evaluates the coordination of fine motor movements of the hand, specifically those that are controlled by the contralateral hemisphere. It is a sensitive measure of the lateralization of motor activity and of the demand for interhemispheric interaction in coordinating bimanual activity (Brinkman & Kuypers, 1973; Brown, 1991; Marion et al., 2003).

On the BCT, straight-line target pathways, varying in angle, appeared on a computer monitor. Subjects maneuvered a cursor through target paths using a response box with two knobs, similar to the Etch-a-Sketch toy (see Figure 1). The left knob controlled horizontal movement and the right knob controlled vertical movement. Target pathways consisted of angles that required only one hand to respond (unimanual left-hand = 0°, and right-hand = 90°), both hands to respond equally (bimanual, symmetrical 45°, 135°), left hand to move faster than the right hand (asymmetrical left dominant = 22.5°, 157.5°), and right hand to move faster than the left hand (asymmetrical right dominant = 67.5°, 112.5°). The protocol consisted of 16 trials: Two trials were performed for each of the pathway angles: 0°, 22.5°, 45°, 67.5°, 90°, 112.5°, 135°, 157.5°.

A description of the outcome measures for the BCT are summarized in Table 1 and are briefly described here. A baseline measure of raw processing speed was calculated by determining the average time to complete the 0° and 90° unimanual (right or left hand only) angles. Next, the average and individual times to complete the bimanual symmetrical (both hands move equally as fast, 45° and 135°), and the bimanual asymmetrical (left dominant, 22.5° and 157.5°; right dominant, 67.5° and 112.5°) angles were computed. Visual motor coordination was calculated

as the speed to complete the bimanual angles relative to unimanual speed. Interhemispheric transfer was calculated by dividing the time for the bimanual asymmetrical angles by the average speed of the bimanual symmetrical angles. The average symmetrical angle time is taken into account when evaluating the asymmetrical angles to control for individual differences in visual-motor coordination. All of the outcome variables were log transformed prior to analysis to reduce skewness.

2.3 Data Analyses

A comparison of the 320 children assessed with the BCT at 16 years and the remaining birth sample (n=443) revealed that the levels of third trimester PAE and PTE differed: 27% of the subjects who participated in this study were exposed to alcohol during third trimester of pregnancy compared to 35% of the non-participants, and the rates of tobacco exposure were 49% and 55%, respectively. Therefore, sample weights were used in the analyses to adjust for the differential loss by third trimester exposure. There were no significant differences between the birth and sample cohorts on race, gender, marijuana or other illicit drug use during pregnancy, maternal education, income, or marital status.

The list of covariates considered in the analyses are summarized in Table 2. The covariates were selected based on a literature review and from an initial bivariate screen of relations between variables. The bivariate relations between PTE, PAE, and PME and the outcome variables were assessed using zero-order correlations: Variables that were significant at $p < 0.10$ were selected for the analyses. Separate stepwise multiple regression models were used to test each of the hypotheses and to control for significant covariates. At each step, the partial correlations between PTE, PAE, and PME and outcome variables and the variance inflation factors were examined to avoid multicollinearity. Interactions were tested to determine if a particular combination of drugs exacerbated the effects. Interactions between PTE, PAE, and PME were assessed by adding the interaction term in the regression as a continuous variable. Each two-way interaction was tested separately. The three-way interaction was not tested to avoid multicollinearity.

In a final step, the validity and adequacy of the fitted regression models were evaluated. The standardized residuals were examined for violations of assumptions and Cook's statistic was used to identify possible outliers or influential data points (Cook et al., 1982). The number of influential data points and outliers ranged from 1 to 4 for the separate variables. Those with influential data points and outliers were removed from the analyses. Removal of these subjects did not affect the overall outcome of the analyses.

3. Results

3.1 Sample Characteristics

Sample characteristics are summarized in Table 2. The sample was 50% male, 45% Caucasian, and had an average monthly household income of \$2043. Seventeen percent of the adolescents did not live with their biological mothers at the time of the interview. For these subjects, the caretakers were interviewed but we will refer to the category generally as mothers. The mothers, on average, had 12 years of education, an IQ of 89, and were 41 years of age. Seventy-two percent of the mothers were working and 38% were married. The average and prevalence of maternal tobacco, alcohol, and marijuana use during pregnancy and at the 16-year assessment phase is summarized in Tables 2 and 3, respectively. The adolescents were 16.75 (16–19) years of age and had an average IQ of 90. Forty percent of the teens had smoked marijuana, 53% had drunk alcohol in the past year, and 28% had smoked tobacco in the last thirty days. Average adolescent drug use is reported in Table 2. Table 3 shows the prevalence of maternal substance use. For descriptive purposes, tobacco, alcohol, and marijuana use were categorized into no

use, light/moderate use (<1 pack/day, <1 drink/day, <1 joint/day), and heavy use (≥ 1 pack/day, ≥ 1 drink/day, ≥ 1 joint/day). In general, women decreased their alcohol and marijuana use across pregnancy. Sixteen percent reported heavy alcohol use during the first trimester compared to 1.4% and 3.4% in the second and third trimesters, respectively, although there were a few women who did not decrease their use across pregnancy. The correlations between the three trimesters ranged from 0.18 to 0.31. Similarly, 13.1%, 5.1%, and 5.0% of the women reported heavy use of marijuana during the first, second, and third trimesters of pregnancy, respectively. The correlation between the three trimesters of marijuana exposure ranged from 0.41 to 0.75. The pattern for tobacco use during pregnancy differed from that of alcohol and marijuana. The rates of heavy tobacco use were 14.4%, 13.7%, and 16.6% for the first, second, and third trimesters, respectively, and cigarette use was highly correlated across the three trimesters, ranging from .82 to .85. In the postpartum, many of the women who abstained from substance use during pregnancy reinstated their use.

Due to the high correlations between trimesters for smoking, it was not possible to separate trimester-specific effects. When we evaluated the effects of trimester-specific alcohol exposure on the BCT outcomes, only the third trimester was significant. Third trimester users were more likely to have been heavier users across pregnancy, so it is not possible to separate the effects of duration from those of dose. Similarly, for marijuana exposure, only the third trimester was significant for all but one variable. Therefore, the results presented below and in the tables are for third trimester exposure, unless otherwise noted.

3.2 Processing Speed

Results for the effects of prenatal and current substance exposure on processing speed are summarized in Table 4. PTE predicted significantly faster processing speed for the 45° angle, a task with low processing demands. PAE predicted significant processing speed deficits on asymmetrical angles 157.5° and 112.5°, tasks with the greatest processing demands that require coordinating the rightward and leftward dominant movements of the hands. First trimester PME predicted slower processing speed for the 22.5° asymmetrical angle.

Current adolescent tobacco use was associated with slower processing speed for several measures including baseline (angle 0°), symmetrical (average and angle 135°), asymmetrical left dominant (average and angle 157.5°), and asymmetrical right dominant (average, and angles 67.5° and 112.5°). Other predictors of slower processing speed included increased adolescent anxiety, more life events, more parental involvement, older mothers, and mother working.

3.3 Visual Motor Coordination

Results for the effects of prenatal and current substance exposure on visual motor coordination are summarized in Table 5. The visual motor coordination assessment is a measure of the ability to coordinate the eyes and hands. PTE and PME predicted better performance on symmetrical movement measures of visual motor coordination. PTE predicted faster reaction times for the 45° angle. PME predicted faster reaction times for the 135° degree angle. There were no significant effects of PAE or current adolescent substance use on visual motor coordination. Right-handedness predicted better performance on measures of visual motor coordination requiring equal movement between the hands and for the measures requiring rightward dominant movement. Higher maternal IQ and current maternal use of alcohol, tobacco, and marijuana also predicted better performance on the visual motor coordination measures.

3.4 Interhemispheric Motor Coordination

Results for the effects of prenatal and current substance exposure on interhemispheric motor coordination (IMC) are summarized in Table 6. PTE predicted deficits on the summary measure

for right hand dominant asymmetrical movement, measured as slower reaction times for the 67.5° angle and slower reaction times for leftward dominant asymmetrical movement for the 22.5° angle. PAE predicted slower reaction times for the summary measure for rightward dominant movement and slower movement on the 112.5° angle. PME was associated with slower reaction time for the summary measure for leftward dominant movement and for the 157.5° angle. Other factors associated with IMC included more maternal anxiety and depressive symptoms, higher maternal IQ, mother working, right handedness, and older adolescent age. More life events and current marijuana use by the adolescent predicted better performance on measures of IMC.

3.5 Interactions between PAE, PTE, and PME

Interactions between PTE, PAE, and PME were assessed using regression analyses to evaluate whether the interaction of the substances would have a greater impact on measures of bimanual coordination than their independent actions. There were no significant interactions.

Other studies have reported associations between PAE and additional measures of IMC transfer (Roebuck et al., 2002; Roebuck-Spencer et al., 2004). These studies, however, did not control for PTE or PME. For three outcome measures of IMC, both tobacco and alcohol predicted deficits in performance (rightward dominant summary variable, 22.5°, and 67.5° angles). We repeated our analyses removing PTE and PME from the regression models for these measures to evaluate whether PAE would be significant in the absence of PTE or PME. There were no outcome measures in which there was overlap between the direct effects of PTE, PAE, and PME.

4. Discussion

This study evaluated the effects of prenatal tobacco, alcohol, and marijuana exposure on bimanual coordination in adolescents. We used a bimanual coordination task that measured unimanual motor speed, visual-motor, and interhemispheric coordination. We found unique effects of PTE, PAE, and PME on processing speed, visual motor coordination, and interhemispheric transfer. Current tobacco use in adolescence also affected processing speed. These effects were independent and there were no significant interactions between PTE, PAE and PME for any outcome.

PTE predicted significantly slower reaction times on measures of interhemispheric transfer on the summary measure, on rightward movement for the 67.5° angle, and on leftward movement for the 22.5° angle. Visual motor coordination was controlled for in these analyses, and therefore does not explain these deficits. PTE was not related to any measure of unimanual motor speed and only one measure of visual-motor coordination (45°).

PAE did not predict deficits on symmetrical bimanual movements, but it was associated with slower processing speed for the most difficult angles that required one hand to move faster than the other hand. Performance of bimanual motor coordination tasks typically degrade as the movements between two limbs become more disparate (Johnson et al., 2000; Rogers et al., 1998). Thus, exposure to PAE was associated with a decrease in the efficiency of bimanual coordination as the tasks became more complex and challenging.

Three studies have reported the effects of PAE on interhemispheric transfer in children with Fetal Alcohol Spectrum Disorder (Dodge et al., 2009; Roebuck et al., 2002; Roebuck-Spencer et al., 2004). Using a similar task as described in this study, Roebuck and colleagues (2002) showed that children with FASD were slower but equally accurate on basic visuomotor tasks, but that as task complexity increased, children with FASD performed worse. Two studies have shown that deficits in performance of a finger localization task are correlated with reductions

in the size of the corpus callosum (Dodge et al., 2009; Roebuck-Spencer et al., 2004). The study by Dodge et al., extended the findings to include to children with moderate exposure to alcohol. Bookstein et al. (2002) demonstrated that a relatively thin corpus callosum was associated with motor functions including poorer balance, poorer motor coordination, more errors and slower to correct errors in hand steadiness, and poorer spatial learning. These studies together demonstrate the relations between prenatal alcohol exposure, corpus callosum dysmorphology, and fine-motor control. The results of the current study are consistent with these reports and suggest that 1) PAE leads to functional brain deficits that underlie the performance of tasks that require interhemispheric performance, and 2) these effects can be detected in a population of adolescents with light to moderate prenatal alcohol exposure.

This study showed PAE related deficits in processing speed on performance of the asymmetrical angles. Several studies have demonstrated similar evidence that prenatal alcohol exposure is associated with slower information processing speed (Kodituwakku, 2007). PAE related deficits in processing speed were demonstrated in infants on the Fagan Test of Infant Intelligence and on a test of visual expectancy (Jacobson, 1998). The Seattle longitudinal cohort reported speed of processing deficits longitudinally at ages four-, seven-, and fourteen (Streissguth et al., 1984; 1986; 1994). Burden et al. (2005) slower reaction times that were associated with performance of a complex cognitive task but not during an automatic processing task (2005). Deficits in processing speed were further linked to timing and amplitude differences on ERP measures implicating brain processing deficits in perceptual processing and stimulus identification/evaluation (Burden et al., 2009). Altogether, these studies show evidence for a primary PAE related deficit in slower processing speed.

The results of this study are consistent with other studies that demonstrate the effects of PAE on fine-motor coordination using other measures. One study, using the Vineland Adaptive Behavior Scales, demonstrated a dose-response effect of prenatal alcohol exposure on fine motor skills in young children (Kalberg et al., 2006). Another study found that childhood motor coordination deficits were only present in adults with the heaviest exposure history and who had multiple neuropsychological deficits as children (Connor et al., 2006). By contrast, we have demonstrated effects at much lower levels.

When we evaluated the effects of trimester-specific alcohol exposure on the BCT outcomes, only the third trimester was significant. The third trimester effects may be most prominent because women who drink in the third trimester were also drinkers in the first and second trimesters, and they drank more heavily compared to women who quit drinking in the first trimester. Alternatively, the measure of third trimester exposure may indicate that this period is critical for these specific PAE effects.

These effects of PAE are likely related to changes in the development of the corpus callosum. The CC connects functionally equivalent cortical areas in each hemisphere. These connections are critical to the integration of sensorimotor functions (Iwamura et al., 1994). The posterior callosum mediates the coordination of information between the hands during bimanual movements and deficits in this area could underlie poorer performance on bimanual motor tasks (Eliassen et al., 1999). The effects of PAE on the CC have been well studied. PAE is associated with specific regional abnormalities in the CC including significant reductions in the anterior and posterior callosal regions (Riley et al., 1995) and displacement of the splenium (Sowell et al., 2001)

Previous studies (Roebuck et al., 2002; Roebuck-Spencer et al., 2004) have shown effects of PAE on interhemispheric transfer, including slower speed to complete unimanual, bimanual, and symmetric angles, that were not found in our analyses. These studies did not consider the effects of PTE or PME. PTE, PAE, and PME were independently associated with specific BCT

outcomes. This highlights the importance of considering all prenatal exposures when trying to understand the independent effects of each drug on development. It is also possible that differences between studies may be due to differences in exposure levels between the studies.

This is the first study to evaluate the effects of PME on processing speed, visual-motor coordination, and interhemispheric transfer using the bimanual coordination task. PME was associated with a decrease in performance on one measure of processing speed (22.5° angle) and two measures of interhemispheric coordination (Avg Left Dominant, and 157.5° angle). There is no precedent in the literature regarding the effects of PME on these cognitive functions. Further research is warranted to better understand the effects of PME on these outcomes.

Potential interactions between PTE, PAE, and PME were evaluated in this study. There were no significant interactions. While there was no interactive effect of PTE and PAE on interhemispheric transfer, each substance independently predicted a slowing of right-to-left transfer suggesting that the right hemisphere projections across the corpus callosum may be impaired. These impairments in interhemispheric transfer that are predicted by PTE and PAE may lead to deficits in attention (Banich, 1998; Rueckert et al., 1994). Both PTE (Cornelius et al., 2001; Fried, 2002; Kotimaa et al., 2003; Leech et al., 1999; Linnet et al., 2003; Linnet et al., 2005; Milberger et al., 1997) and PAE (Coles et al., 1997; Mattson et al., 1999; Streissguth et al., 1986; Streissguth et al., 1989; Streissguth et al., 1994) have been shown to have long-term effects on attention.

Current adolescent tobacco use was associated with a deficit in processing speed that is correlated with other cognitive skills and to higher-order cognitive processes such as short-term memory (Hale, 1990; Kail, 1991; Kail & Ferrer, 2007; Kail & Park, 1994; Kail & Salthouse, 1994; Rabbitt & Goward, 1994). This finding converges with research showing that current tobacco use in adolescents is associated with alterations in working memory, receptive and expressive vocabulary, oral arithmetic, and auditory memory (Fried et al., 2006; Jacobsen et al., 2005). Jacobsen and colleagues have reported separate effects of prenatal and current tobacco use on measures of attention (Jacobsen, Slotkin et al., 2007) and working memory (Jacobsen, Mencl et al., 2007; Jacobsen et al., 2006). Their studies and ours document the separate and independent effects of prenatal and current tobacco exposure on cognitive ability.

Our results are consistent with previous studies of PAE on interhemispheric transfer, although there are important differences between the studies. Our study prospectively assessed prenatal alcohol exposure in a sample of 320 adolescents of low socioeconomic status, the majority of whom has low to moderate levels of exposure. Previous studies were done in much smaller samples and in children with heavier alcohol exposure that was evaluated retrospectively. Importantly, the current study also assessed covariates, such as demographics, home environment, psychological status of the mother and child, and current substance use, which allowed us to understand the larger context for the effects of PTE, PAE, and PME on bimanual coordination.

The amount of additional variance predicted by prenatal exposure to tobacco, alcohol, and marijuana was significant but small. Thus, the relation between prenatal substance exposure and measures of performance of the bimanual coordination task explains only a small portion of the overall variability. However, this is a portion of the variability that could be prevented.

This study showed that 1) prenatal alcohol, tobacco, and marijuana exposure separately and significantly predicted deficits in bimanual coordination and movement, and 2) these effects were found at light to moderate levels of exposure. We also demonstrated the importance of considering other exposures when determining the direct effect of any one substance on measures of cognitive function. This inefficient processing within and between hemispheres has significant implications for both cognitive, behavioral, and psychological function,

particularly as information increases in complexity. Further study is warranted to identify the underlying cause of deficits in bimanual coordination measures in prenatally drug-exposed adolescents

Acknowledgments

This research is supported by the National Institute on Alcohol Abuse and Alcoholism (AA 06666, Principal Investigator, N.L. Day, Ph.D.) and National Institute on Drug Abuse (DA 003874, Principal Investigator, N.L. Day, Ph.D.).

References

1. Anthony B, Zhou FC, Ogawa T, Goodlett CR, Ruiz J. Alcohol exposure alters cell cycle and apoptotic events during early neurulation. *Alcohol* 2008;43:261–273. [PubMed: 18283098]
2. Banich MT. The missing link: the role of interhemispheric interaction in attentional processing. *Brain Cognitive* 1998;36:128–157.
3. Barr HM, Streissguth AP, Darby BL, Sampson PD. Prenatal exposure to alcohol, caffeine, tobacco, and aspirin: Effects on fine and gross motor performance in 4-year-old children. *Dev. Psychol* 1990;26:339–348.
4. Batstra L, Neeleman J, Haddars-Algra M. Can breast feeding modify the adverse effects of smoking during pregnancy on the child's cognitive development? *J Epidemiol Commun H* 2003;57:403–404.
5. Bookstein FL, Streissguth AP, Sampson PD, Connor PD, Barr HM. Corpus callosum shape and neuropsychological deficits in adult males with heavy fetal alcohol exposure. *Neuroimage* 2002;15:233–251. [PubMed: 11771992]
6. Brinkman J, Kuypers HGJM. Cerebral control of contralateral and ipsilateral arm, hand, and finger movements in split-brain rhesus monkey. *Brain* 1973;96:653–673. [PubMed: 4204228]
7. Brooke OG, Anderson HR, Bland JM, Peacock JL, Stewart CM. Effects on birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. *BMJ* 1989;298:795–801. [PubMed: 2496859]
8. Brown, WS. The Bimanual Coordination Test: Version 1. Pasadena, CA: The Travis Institute; 1991.
9. Brown SA, Tapert SF, Granholm E, Delis DC. Neurocognitive functioning of adolescents: effects on protracted alcohol use. *Alcohol. Clin. Exp. Res* 2000;24:164–171. [PubMed: 10698367]
10. Burden MJ, Andrew C, Saint-Amour D, Meintjes EM, Molteno CD, Hoyme HE, Robinson LK, Khaole N, Nelson CA, Jacobson JL, Jacobson SW. The effects of fetal alcohol syndrome on response execution and inhibition: an event-related potential study. *Alcohol. Clin. Exp. Res* 2009;33:1994–2004. [PubMed: 19719791]
11. Burden MJ, Jacobson SW, Jacobson JL. Relation of prenatal alcohol exposure to cognitive processing speed and efficiency in childhood. *Neurotoxicol. Teratol* 2005;29:1473–1483.
12. CDC, Center for Disease Control and Prevention. Alcohol use among women of childbearing age—United States 1991–1999. *MMWR* 2002a;51:273–276.
13. CDC, Center for Disease Control and Prevention. Prevalence of selected maternal behaviors and experiences. Pregnancy Risk Assessment Monitoring System (PRAMS) 1999. *MMWR* 2002b;51:1–27.
14. Chandler LS, Richardson GA, Gallagher JD, Day NL. Prenatal exposure to alcohol and marijuana: effects on motor development of preschool children. *Alcohol. Clin. Exp. Res* 1996;20:455–461. [PubMed: 8727237]
15. Clark DB, Kirisci L. Posttraumatic stress disorder, depression, alcohol use disorders and quality of life in adolescents. *Anxiety* 1996;2:226–233. [PubMed: 9160627]
16. Coles C, Platzman K, Raskind-Hood C, Brown R, Falek A, Smith I. A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. *Alcohol. Clin. Exp. Res* 1997;21:150–161. [PubMed: 9046388]
17. Collins CC, Grella CE, Hser YI. Effects of gender and level of parental involvement among parents in drug treatment. *Am. J. Drug Alcohol. Abuse* 2003;29:237–261. [PubMed: 12765205]

18. Connor PD, Sampson PD, Bookstein FL, Barr HM, Streissguth AP. Direct and indirect effects of prenatal alcohol damage on executive function. *Dev. Neuropsychol* 2000;18:331–354. [PubMed: 11385829]
19. Connor PD, Sampson PD, Streissguth AP, Bookstein FL, Barr HM. Effects of prenatal alcohol exposure on fine motor coordination and balance: A study of two adult samples. *Neuropsychologia* 2006;44:744–751. [PubMed: 16154165]
20. Cook, RD.; Weisberg, S. Residuals and influence in regression. New York, NY: Chapman and Hall; 1982.
21. Cornelius, M.; Day, N.; Richardson, G.; Taylor, P. Epidemiology of substance abuse during pregnancy. In: Ott, P.; Tarter, R.; Ammerman, R., editors. *Sourcebook on Substance Abuse: Etiology, Epidemiology, Assessment and Treatment*. Needham Heights, MA: Allyn and Bacon; 1999. p. 1-13.
22. Cornelius M, Ryan C, Day N, Goldschmidt L, Willford J. Prenatal tobacco effects on neuropsychological outcomes among preadolescents. *J. Dev. Behav. Pediatr* 2001;22:217–225. [PubMed: 11530894]
23. Day NL, Cotreau CM, Richardson GA. The epidemiology of alcohol, marijuana, and cocaine use among women of childbearing age and pregnant women. *Clin. Obstet. Gynecol* 1993;36:232–245. [PubMed: 8513621]
24. Dempsey DA, Hajnal BL, Partridge JC, Jacobson SN, Good W, Jones RT, Ferriero DM. Tone abnormalities are associated with maternal cigarette smoking during pregnancy *in utero* cocaine-exposed infants. *Pediatrics* 2000;106:79–85. [PubMed: 10878153]
25. Dew PC, Guillory VJ, Okah FA, Cai J, Hoff GL. The effect of health compromising behaviors on preterm births. *Matern. Child. Health. J* 2007;11:227–233. [PubMed: 17136459]
26. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics* 2004;113:1007–1015. [PubMed: 15060193]
27. Dodge NC, Jacobson JL, Moltano CD, Meintjes EM, Bangalore S, Diwadkar V, Hoyme EH, Robinson LK, Khaole N, Avison MJ, Jacobson SW. Prenatal alcohol exposure and interhemispheric transfer of tactile information: Detroit and Cape Town findings *Alcohol. Clin. Exp. Res* 2009;33:1628–1637.
28. Dohrenwend BS, Krasnoff L, Askenasy AR, Dohrenwend BP. Exemplification of a method for scaling life events: the Peri Life Events Scale. *J. Health. Soc. Behav* 1978;19:205–229. [PubMed: 681735]
29. Druse, MJ. Effects of in utero ethanol exposure on the development of neurotransmitter systems. Wilmington, DE: Wiley-Liss, Inc; 1992.
30. Ebrahim SH, Decoufle P, Palakathodi AS. Combined tobacco and alcohol use by pregnant and reproductive-aged women in the United States. *Obstet. Gynecol* 2000;96:767–771. [PubMed: 11042316]
31. Ebrahim SH, Gfroerer J. Pregnancy related substance use in the United States during 1996–1998. *Obstet. Gynecol* 2003;101:374–379. [PubMed: 12576263]
32. Eliassen JC, Baynes K, Gazzaniga MS. Direction information coordinated via the posterior third of the corpus callosum during bimanual movements. *Exp. Brain. Res* 1999;128:573–577. [PubMed: 10541755]
33. Eskenazi B, Castorina R. Association of prenatal maternal or postnatal child environmental tobacco smoke exposure and neurodevelopmental and behavioral problems in children. *Environ. Health Perspect* 1999;107:991–1000. [PubMed: 10585903]
34. Floyd RL, Decoufle P, Hungerford DW. Alcohol use prior to pregnancy recognition. *Am. J. Prev. Med* 1999;17:101–107. [PubMed: 10490051]
35. Fried PA. Adolescents prenatally exposed to marijuana: examination of facets of complex behaviors and comparisons with the influence of in utero cigarettes. *J. Clin. Pharmacol* 2002;42:97S–102S. [PubMed: 12412842]
36. Fried PA, Smith AM. A literature review of the consequences of prenatal marijuana exposure. An emerging theme of a deficiency in aspects of executive function. *Neurotoxicol. Teratol* 2001;1:1–11.
37. Fried P, Watkinson B. Visuo-perceptual functioning differs in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol. Teratol* 2000;22:11–20. [PubMed: 10642110]

38. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol. Teratol* 2003;25:427–436. [PubMed: 12798960]
39. Fried PA, Watkinson B, Gray R. Neurocognitive consequences of cigarette smoking in young adults-- a comparison with pre-drug performance. *Neurotoxicol. Teratol* 2006;28:517–525. [PubMed: 16904287]
40. Fried P, Watkinson B, Siegel L. Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol. Teratol* 1997;19:171–183. [PubMed: 9200137]
41. Goldschmidt L, Richardson GA, Stoffer DS, Geva D, Day NL. Prenatal alcohol exposure and academic achievement at age six: a nonlinear fit. *Alcohol. Clin. Exp. Res* 1996;20:763–770. [PubMed: 8800397]
42. Goldschmidt L, Richardson GA, Cornelius MD, Day NL. Prenatal marijuana and alcohol exposure and academic achievement at age 10. *Neurotoxicol. Teratol* 2004;26:521–532. [PubMed: 15203174]
43. Goodlett CR, Horn KH. Mechanisms of alcohol-induced damage to the developing nervous system. *Alcohol Res. Health* 2001;25:175–184. [PubMed: 11810955]
44. Hale S. A global developmental trend in cognitive processing speed. *Child Dev* 1990;61:653–663. [PubMed: 2364741]
45. Hall LA, Gurley DN, Sachs B, Kryscio RJ. Psychosocial predictors of maternal depressive symptoms, parenting attitudes, and child behavior in single-parent families. *Nurs. Res* 1991;40(4):214–220. [PubMed: 1857646]
46. Harkany T, Guzman M, Galve-Roperh I, Berghuis P, Devi LA, Mackie K. The emerging functions of endocannabinoid signaling during CNS development. *Trends Pharmacol. Sci* 2007;28:83–92. [PubMed: 17222464]
47. Haste FM, Anderson HR, Brooke OG, Bland JM, Peacock JL. The effects of smoking and drinking on the anthropometric measurements of neonates. *Paediatr. Perinat. Epidemiol* 1991;5:83–92. [PubMed: 2000340]
48. Howell KK, Lynch ME, Platzman KA, Smith GH, Coles CD. Prenatal alcohol exposure and ability, academic achievement, and school functioning in adolescence: a longitudinal follow-up. *J. Pediatr. Psychol* 2006;31:116–126. [PubMed: 15829611]
49. Iwamura Y, Iriki A, Tanaka M. Bilateral hand representation in the postcentral somatosensory cortex. *Nature* 1994;369:554–556. [PubMed: 8202155]
50. Jacobsen LK, Krystal JH, Mennel WE, Westerveld M, Frost SJ, Pugh KR. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. *Biol. Psychiatry* 2005;57:56–66. [PubMed: 15607301]
51. Jacobsen LK, Mennel WE, Constable RT, Westerveld M, Pugh KR. Impact of smoking abstinence on working memory neurocircuitry in adolescent daily tobacco smokers. *Psychopharmacology* 2007;193:557–566. [PubMed: 17505817]
52. Jacobsen LK, Slotkin TA, Mennel WE, Frost SJ, Pugh KR. Gender-specific effects of prenatal and adolescent exposure to tobacco smoke on auditory and visual attention. *Neuropsychopharmacology* 2007;32:2453–2464. [PubMed: 17375135]
53. Jacobsen LK, Slotkin TA, Westerveld M, Mennel WE, Pugh KR. Visuospatial memory deficits emerging during nicotine withdrawal in adolescents with prenatal exposure to active maternal smoking. *Neuropsychopharmacology* 2006;31:1550–1561. [PubMed: 16341023]
54. Jacobson SW. Specificity of neurobehavioral outcomes associated with prenatal alcohol exposure. *Alcohol. Clin. Exp. Res* 1998;22:313–320. [PubMed: 9581634]
55. Kahn RS, Khoury J, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. *J. Pediatr* 2003;143:104–110. [PubMed: 12915833]
56. Kail R. Developmental change in speed of processing during childhood and adolescence. *Psychol. Bull* 1991;109:490–501. [PubMed: 2062981]
57. Kail RV, Ferrer E. Processing speed in childhood and adolescence: longitudinal models for examining developmental change. *Child Dev* 2007;78:1760–1770. [PubMed: 17988319]
58. Kail R, Park YS. Processing time, articulation time, and memory span. *J. Exp. Child Psychol* 1994;57:281–291. [PubMed: 8169582]

59. Kail R, Salthouse TA. Processing speed as a mental capacity. *Acta Psychol* 1994;86:199–225.
60. Kalberg WO, Provost B, Tollison SJ, Tabachnick BG, Robinson LK, Eugene Hoyme H, Trujillo PM, Buckley D, Aragon AS, May PA. Comparison of motor delays in young children with fetal alcohol syndrome to those with prenatal alcohol exposure and with no prenatal alcohol exposure. *Alcohol. Clin. Exp. Res* 2006;30:2037–2045. [PubMed: 17117969]
61. Kawashima R, Yamada K, Kinomura S, Yamaguchi T, Matsui H, Yoshioka S, Fukuda H. Regional cerebral blood flow changes of cortical motor areas and prefrontal areas in humans related to ipsilateral and contralateral hand movement. *Brain Res* 1993;623:33–40. [PubMed: 8221091]
62. Kodituwakku PW. Defining the behavioral phenotype in children with fetal alcohol spectrum disorders: a review. *Neurosci. Biobehav. Rev* 2007;31:192–201. [PubMed: 16930704]
63. Kotimaa A, Moilanen I, Taanila A, Ebeling H, Smalley S, McGough J, Hartikainen A, Jarvelin M. Maternal smoking and hyperactivity in 8-year-old children. *J. Am. Acad. Child Adol. Psych* 2003;42:826–833.
64. Kovacs M, Goldston D. Cognitive and social cognitive development of depressed children and adolescents. *J. Am. Acad. Child Psy* 1991;30:388–392.
65. Landry SH, Smith KE, Swank PR. Responsive parenting: establishing early foundations for social, communication, and independent problem-solving skills. *Dev. Psychol* 2006;42:627–642. [PubMed: 16802896]
66. LeClere FB, Wilson JB. Smoking behavior of recent mothers, 18–44 years of age, before and after pregnancy: United States. *Adv. Data* 1997;288:1–11. [PubMed: 10182807]
67. Leech SL, Richardson G, Goldschmidt L, Day N. Prenatal substance exposure: effects on attention and impulsivity of 6-year-olds. *Neurotoxicol Teratol* 1999;21:109–118. [PubMed: 10192271]
68. Levin, ED.; Slotkin, TA. Developmental neurotoxicity of nicotine. In: Slikker, W.; Chang, LW., editors. *Handbook of Developmental Neurotoxicology*. San Diego, CA: Academic Press; 1998. p. 587–615.
69. Levitt P. Prenatal effects of drugs of abuse on brain development. *Drug Alcohol Depend* 1998;51:109–125. [PubMed: 9716934]
70. Linnet KM, Dalsgaard S, Obel C, Wisborg K, Henriksen T, Rodriguez A, Kotimaa A, Moilanen I, Thomsen P, Olsen J, Jarvelin M. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am. J. Psychiatry* 2003;160:1028–1040. [PubMed: 12777257]
71. Linnet KM, Wisborg K, Obel C, Secher N, Thomsen P, Agerbo E, Henriksen T. Smoking during pregnancy and the risk for hyperkinetic disorder in offspring. *Pediatrics* 2005;116:462–467. [PubMed: 16061604]
72. Locke TF, Newcomb M. Child maltreatment, parent alcohol and drug-related problems, polydrug problems, and parenting practices: a test of gender differences and four theoretical perspectives. *J. Fam. Psychol* 2004;18:120–134. [PubMed: 14992615]
73. Lutenbacher M, Hall LA. The effects of maternal psychosocial factors on parenting attitudes of low-income, single mothers with young children. *Nurs. Res* 1998;47:25–34. [PubMed: 9478181]
74. Malanga CJ, Kosofsky BE. Mechanisms of action of drugs of abuse on the developing fetal brain. *Clin. Perinatol* 1999;26:17–37. [PubMed: 10214541]
75. Marion SD, Kilian SC, Naramor TL, Brown WS. Normal development of bimanual coordination: visuomotor and interhemispheric contributions. *Dev. Neuropsychol* 2003;23:399–421. [PubMed: 12740193]
76. Mattson SN, Goodman AM, Caine C, Delis DC, Riley EP. Executive functioning in children with heavy prenatal alcohol exposure. *Alcohol. Clin. Exp. Res* 1999;23:1808–1815. [PubMed: 10591598]
77. Mattson SN, Riley EP, Gramling L, Delis DC, Jones KL. Neuropsychological comparison of alcohol-exposed children with or without physical features of fetal alcohol syndrome. *Neuropsychology* 1998;12:146–153. [PubMed: 9460742]
78. Milberger S, Biederman J, Faraone S, Chen L, Jones J. Further evidence of an association between attention-deficit/hyperactivity disorder and cigarette smoking. Findings from a high-risk sample of siblings. *Am. J. Addict* 1997;6:205–217. [PubMed: 9256986]
79. Miller MW. Migration of cortical neurons is altered by gestational exposure to ethanol. *Alcohol. Clin. Exp. Res* 1993;17:304–314. [PubMed: 8488973]

80. Miller MW. Effect of early exposure to ethanol on the protein and DNA contents of specific brain regions in the rat. *Brain Res* 1996;734:286–294. [PubMed: 8896836]
81. Miller MW, Dow-Edwards DL. Structural and metabolic alterations in rat cerebral cortex induced by prenatal exposure to ethanol. *Brain Res* 1988;474:316–326. [PubMed: 3208136]
82. Miller MW, Nowakowski RS. Effect of prenatal exposure to ethanol on the cell cycle kinetics and growth fraction in the proliferative zones of fetal rat cerebral cortex. *Alcohol. Clin. Exp. Res* 1991;15:229–232. [PubMed: 2058800]
83. Miller MW, Potempa G. Numbers of neurons and glia in mature rat somatosensory cortex: effects of prenatal exposure to ethanol. *J. Comp. Neurol* 1990;293:92–102. [PubMed: 2312794]
84. Miller-Loncar C, Lester BM, Seifer R, Lagasse LL, Bauer CR, Shankaran S, Bada HS, Wright LL, Smeriglio VL, Bigsby R, Liu J. Predictors of motor development in children prenatally exposed to cocaine. *Neurotoxicol. Teratol* 2005;27:213–220. [PubMed: 15734272]
85. Moser RP, Jacob T. Parent-child interactions and child outcomes as related to gender of alcoholic parent. *J. Subst. Abuse* 1997;9:189–208. [PubMed: 9494949]
86. NCI, National Cancer Institute. Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California Environmental Protection Agency. 1999.
87. Olsen J, Pereira AC, Olsen SF. Does maternal tobacco smoking modify the effect of alcohol on fetal growth? *Am. J. Public Health* 1991;81:69–73. [PubMed: 1983919]
88. Pennington, SN. Ethanol-induced teratology and second messenger signal transduction. In: Miller, MW., editor. *Development of the central nervous system: Effects of alcohol and opiates*. New York, NY: John Wiley and Sons; 1992. p. 189-208.
89. Pentney, RJ.; Miller, MW. Effects of ethanol on neuronal morphogenesis. In: Miller, MW., editor. *Development of the central nervous system: Effects of alcohol and opiates*. New York, NY: Wiley-Liss, Inc; 1992. p. 71-107.
90. Puig-Antich J, Lukens E, Davies M, Goetz D, Brennan-Quattrock J, Todak G. Psychosocial functioning in prepubertal major depressive disorders. I. Interpersonal relationships during the depressive episode. *Arch. Gen. Psychiat* 1985;42:500–507. [PubMed: 3985760]
91. Rabbitt P, Goward L. Age, information processing speed, and intelligence. *Q. J. Exp. Psychol* 1994;47:741–760.
92. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *App. Psychol. Meas* 1977;1:385–401.
93. Ramanathan R, Wilkemeyer MF, Mittal B, Perides G, Charness ME. Alcohol inhibits cell-cell adhesion mediated by human L1. *J. Cell Biol* 1996;133:381–390. [PubMed: 8609170]
94. Richardson GA, Day NL, Goldschmidt L. Goldschmidt, Prenatal alcohol, marijuana, and tobacco use: infant mental and motor development. *Neurotoxicol. and Teratol* 1995;4:479–487.
95. Richardson GA, Ryan C, Willford J, Day NL, Goldschmidt L. Prenatal alcohol and marijuana exposure: effects on neuropsychological outcomes at 10 years. *Neurotoxicol. Teratol* 2002;24:309–320. [PubMed: 12009486]
96. Riley EP, Mattson SN, Sowell ER, Jernigan TL, Sobel DF, Jones KL. Abnormalities of the corpus callosum in children prenatally exposed to alcohol. *Alcohol. Clin. Exp. Res* 1995;19:1198–1202. [PubMed: 8561290]
97. Roebuck-Spencer TM, Mattson SN, Marion SD, Brown WS, Riley EP. Bimanual coordination in alcohol-exposed children: role of the corpus callosum. *J. Int. Neuropsychol. Soc* 2004;10:536–548. [PubMed: 15327732]
98. Roebuck TM, Mattson SN, Riley EP. Interhemispheric transfer in children with heavy prenatal alcohol exposure. *Alcohol. Clin. Exp. Res* 2002;26:1863–1871. [PubMed: 12500111]
99. Rueckert L, Sorensen L, Levy J. Callosal efficiency is related to sustained attention. *Neuropsychologia* 1994;32:159–173.
100. Scheier LM, Botvin GJ. Effects of early adolescent drug use on cognitive efficacy in early-late adolescence: a developmental structural model. *J. Subst. Abuse* 1995;7:379–404. [PubMed: 8838623]
101. Shu XO, Hatch MC, Mills J, Clemens J, Susser M. Maternal smoking, alcohol drinking, caffeine consumption, and fetal growth: results from a prospective study. *Epidemiology* 1995;6:115–120. [PubMed: 7742395]

102. Slotkin, TA. Prenatal exposure to nicotine: what can we learn from animal models?. In: Zagon, IS.; Slotkin, TA., editors. *Maternal substance abuse and the developing nervous system*. San Diego, CA: Academic Press; 1992. p. 97-124.
103. Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? *J. Pharmacol. Exp. Ther* 1998;285:931–945. [PubMed: 9618392]
104. Slotkin TA. Developmental cholinotoxicants: nicotine and chlorpyrifos. *Environ. Health. Perspect* 1999;107:71–80. [PubMed: 10229709]
105. Smith KE, Landry SH, Swank PR. The role of early maternal responsiveness in supporting school-aged cognitive development for children who vary in birth status. *Pediatrics* 2006;117:1608–1617. [PubMed: 16651314]
106. Sowell ER, Mattson SN, Thompson PM, Jernigan TL, Riley EP, Toga AW. Mapping callosal morphology and cognitive correlates: effects of heavy prenatal alcohol exposure. *Neurology* 2001;57:235–244. [PubMed: 11468307]
107. Spielberger, CD. Preliminary manual for the State-Trait Personality Inventory (STPI). FL: University of South Florida; 1979.
108. Streissguth AP, Barr H, Olson H, Sampson P, Bookstein F, Burgess D. Drinking during pregnancy decreases word attack and arithmetic scores on standardized tests: adolescent data from a population-based prospective study. *Alcohol. Clin. Exp. Res* 1994;18:248–254. [PubMed: 8048722]
109. Streissguth AP, Barr H, Sampson P, Parrish-Johnson J, Kirchner G, Martin D. Attention distraction and reaction time at age 7 years and prenatal alcohol exposure. *Neurotoxicol Teratol* 1986;8:717–725.
110. Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. *Develop. Behav. Ped* 2004;25:228–238.
111. Streissguth AP, Bookstein F, Sampson P, Barr H. Neurobehavioral effects of prenatal alcohol: Part III. PLS analyses of neuropsychologic tests. *Neurotoxicol. Teratol* 1989;11:493–507. [PubMed: 2593988]
112. Streissguth AP, Martin DC, Barr HM, Sandman BM. Intrauterine alcohol and nicotine exposure: Attention and reaction time in 4-year-old children. *Dev Psychol* 1984;20:533–541.
113. Streissguth AP, Sampson PD, Olson HC, Bookstein FL, Barr HM, Scott M, Feldman J, Mirsky AF. Maternal drinking during pregnancy: Attention and short-term memory in 14-year-old offspring: a longitudinal prospective study. *Alcohol. Clin. Exp. Res* 1994;18:202–218. [PubMed: 8198221]
114. Steinberg L, Lamborn S, Dornbusch S, Darling N. Impact of parenting practices on adolescent achievement: Authoritative parenting, school involvement, and encouragement to succeed. *Child Dev* 1992;63:1266–1281. [PubMed: 1446552]
115. Tapert SF, Granholm E, Leedy NG, Brown SA. Substance use and withdrawal: neuropsychological functioning over 8 years in youth. *J. Int. Neuropsychol. Soc* 2002;8:873–883. [PubMed: 12405538]
116. Tong S, Baghurst P, Vimpani G, McMichael A. Socioeconomic position, maternal IQ, home environment, and cognitive development. *J. Pediatr* 2007;151:284–288. [PubMed: 17719939]
117. U.S. Department of Health and Human Services. Advance report number 10. Rockville, MD: Substance Abuse and Mental Health Services Administration; 1995. Preliminary estimates from the 1994 national household survey on drug abuse.
118. Wechsler, D. Wechsler Adult Intelligence Scale--Revised. New York, NY: Psychological Corporation; 1981.
119. West JR, Chen WJ, Pantazis NJ. Fetal alcohol syndrome: the vulnerability of the developing brain and possible mechanisms of damage. *Metab. Brain Dis* 1994;9:291–322. [PubMed: 7898398]
120. Willford JA, Richardson GA, Leech SL, Day NL. Verbal and visuospatial learning and memory function in children with moderate prenatal alcohol exposure. *Alcohol. Clin. Exp. Res* 2004;28:497–507. [PubMed: 15084908]
121. Zhou FC, Sari Y, Powrozek T, Goodlett CR, Li TK. Moderate alcohol exposure compromises neural tube midline development in prenatal brain. *Brain Res. Dev. Brain Res* 2003;144:43–55.

Figure 1.

Schematic of the target pathways and response box for the computerized Bimanual Coordination Test. The target paths appear on a computer screen and the response box sits on a table in front of the subject. The right knob on the response box controls vertical movement while the left knob controls horizontal movement. Bimanual performance on paths were grouped for analyses into those requiring (1) unimanual movement (0° and 90°), (2) symmetrical movement (both hands moving at the same rate, 45° and 135°), (3) Rightward dominant movement (right hand must move faster than the left, 67.5° and 112.5°), and (4) Leftward dominant movement (left hand must move faster than the right, 22.5° and 157.5°). Response time was recorded as the number of seconds to complete the path.

Table 1

Description of the Outcome Measures for the Bimanual Coordination Task

Three types of movement were examined:	
Unimanual:	Movement with one hand only.
Symmetrical:	Movement that was equal between the right and left hands.
Asymmetrical:	Movement in which one hand must move faster than the other.
Three measures were calculated:	
Processing Speed:	Average unimanual speed. Includes the 0° and 90° degree angles.
Visual Motor Coordination:	Bimanual speed/Unimanual Speed
	The bimanual angles require equal movement by both hands. The following measures were evaluated: <i>Time 45°/Avg Time for 0° and 90°</i> <i>Time 135°/Avg Time for 0° and 90°</i>
Interhemispheric Transfer:	Asymmetrical angle time/Symmetrical angle time
	The asymmetrical angles require that one hand move faster than the other. The following measures were evaluated: Rightward dominant movement: <i>Time 67.5°/Avg Time for 45° and 135°</i> <i>Time 112.5°/Avg Time for 45° and 135°</i> <i>Time 22.5°/Avg Time for 45° and 135°</i> <i>Time 157.5°/Avg Time for 45° and 135°</i>

Table 2**Sample Characteristics**

	Mean (Range)
<u>Demographics</u>	
Sex (% Male)	50
Race (% White)	45
Maternal IQ	89 (61–120)
Average Household Income	2043 (0–9990)
Number of Life Events	3 (0–12)
<u>Maternal Characteristics</u>	
Education (Years)	12 (7–18)
Work Status (% Working)	72
Age (includes caregivers)	41 (22–68)
Marital Status (% Married)	38
Depression (CES-D)	39 (20–69)
Anxiety (STPI)	17 (10–40)
Hostility	16 (10–36)
<u>Adolescent Characteristics</u>	
Age	16.75 (16–19)
Handedness (% Right)	89.2
Depression (CDI)	43 (34–93)
Anxiety (RCMAS)	5.9 (0–26)
Current Substance Exposure (includes users only)	
Tobacco (Avg Cigarettes/Day)	5.30 (.01–20)
Alcohol (Avg Daily Volume)	0.50 (.01–17.42)
Marijuana (Avg Daily Joints)	0.40 (.00001 – 5.33)
Other Illicit Drug Use (% use)	8.7
Adolescent IQ	
Full Scale	90 (49–131)
Verbal	90 (54–129)
Performance	92 (53–139)
<u>Prenatal Substance Exposure</u>	
(includes users only)	
Alcohol (Average Daily Volume)	
First Trimester	0.75 (0.007–6.68)
Second Trimester	0.26 (0.01–6.18)
Third Trimester	0.32 (0.02–3.2)
Tobacco (Average Cigarettes/Day)	
First Trimester	14.5 (0.50–50)
Second Trimester	15.3 (0.50–70)
Third Trimester	16.7 (0.50–50)
Marijuana (Average Daily Joints)	

	Mean (Range)
First Trimester	0.99 (0.003–8.8)
Second Trimester	0.70 (0.01–6.5)
Third Trimester	0.79 (0.01–9.4)

Table 3

Prevalence of Maternal Tobacco, Alcohol, and Marijuana Use (%)

Tobacco Use				
Time of Assessment	None ^a	Light/Moderate ^b	Heavy ^c	Total n ^d
First trimester	48.1	37.5	14.4	320
Second trimester	50.3	36.0	13.7	292
Third trimester	50.9	32.5	16.6	320
16 years	46.2	35.3	18.4	320
Alcohol Use				
Time of Assessment	None ^a	Light/Moderate ^b	Heavy ^c	Total n ^d
First trimester	38.4	45.3	16.3	320
Second trimester	66.7	32.0	1.4	291
Third trimester	72.5	24.1	3.4	320
16 years	22.8	52.8	24.4	320
Marijuana Use				
Time of Assessment	None ^a	Light/Moderate ^b	Heavy ^c	Total n ^d
First trimester	58.7	28.2	13.1	320
Second trimester	77.4	17.4	5.1	292
Third trimester	79.7	15.3	5.0	320
16 years	85.6	11.6	2.8	320

^aNone: no use^bLight/moderate: Tobacco (<1 pack/day), Alcohol (<1 drink/day), Marijuana (<1 joint/day).^cHeavy: Tobacco (≥1 pack/day), Alcohol (≥1 drink/day), Marijuana (≥1 joint/day).^dSample sizes differ due to missing data

Effects of Prenatal and Current Tobacco, Alcohol, and Marijuana Use on Processing Speed on the Bimanual Coordination Task

Table 4

BCT Outcome Measures	Mean (SD)	Prenatal Effects		Adolescent Use at 16			
		Predictor	Beta	P	Predictor	Beta	P
Summary Variables							
Avg Baseline (time 0°, time 90°)	7.42 (2.06)	---	---	---	---	---	**
Avg Symmetrical (time 45°, time 135°)	13.48 (5.27)	---	---	---	Tobacco	0.01	**
Avg Left Dominant (time 22.5°, time 157.5°)	12.72 (4.72)	---	---	---	Tobacco	0.02	**
Avg Right Dominant (time 67.5°, time 112.5°)	13.22 (4.50)	---	---	---	Tobacco	0.01	**
Baseline Angles							
time 0°	8.18 (2.88)	---	---	---	Tobacco	0.01	*
time 90°	6.67 (1.94)	---	---	---	---	---	---
Symmetrical Angles							
time 45°	12.03 (4.82)	Tobacco	-0.004	---	---	---	---
time 135°	14.70 (6.91)	---	---	*	Tobacco	0.01	*
Asymmetrical Angles: Left Dominant							
time 22.5°	12.00 (4.68)	Marijuana	0.09	*	---	---	---
time 157.5°	13.28 (5.51)	Alcohol	0.17	*	Tobacco	0.01	**
Asymmetrical Angles: Right Dominant							
time 67.5°	13.07 (4.93)	---	---	---	Tobacco	0.01	*
time 112.5°	13.28	Alcohol	0.32	---	Tobacco	0.01	**

BCT Outcome Measures	Mean (SD)	Prenatal Effects		Adolescent Use at 16	
		Predictor	Beta	Predictor	Beta
	(5.09)				

* p<.05,
** p<.01,
*** p<.001

Table 5
Prenatal and Current Tobacco, Alcohol, and Marijuana Effects on Visual Motor Coordination

BCT Outcome Measures	Mean (SD)	Prenatal Effects		Adolescent Use at 16			
		Predictor	Beta	P	Predictor	Beta	P
Summary Variables							
Avg Symmetrical (mean 45°, 135°/mean 0°, 90°)	1.88 (.75)	---	---	---	---	---	
Avg Left Dominant (mean 22.5°, 157.5°/mean 0°, 90°)	1.78 (.65)	---	---	---	---	---	
Avg Right Dominant (mean 67.5°, 112.5°/mean 0°, 90°)	1.85 (.64)	---	---	---	---	---	
Symmetrical Angles							
45° (45°/ mean 0°, 90°)	1.69 (.68)	Tobacco	---	***	---	---	
135° (135°/ mean 0°, 90°)	2.03 (.93)	Marijuana	0.01	**	---	---	
		---	---	---	---	---	
			0.18				
Asymmetrical Angles: Left Dominant							
22.5° (22.5°/ mean 0°, 90°)	1.68 (.74)	---	---	---	---	---	
157.5° (157.5°/ mean 0°, 90°)	1.85 (.72)	---	---	---	---	---	
Asymmetrical Angles: Right Dominant							
67.5° (67.5°/ mean 0°, 90°)	1.83 (.75)	---	---	---	---	---	
112.5° (112.5°/ mean 0°, 90°)	1.85 (.75)	---	---	---	---	---	

* p<.05,

** p<.01,

*** p<.001

Table 6

Summary of Prenatal and Current Tobacco, Alcohol, and Marijuana Use Effects on Interhemispheric Coordination

BCT Outcome Measures	Mean (SD)	Prenatal Effects		Adolescent Use at 16			
		Predictor	Beta	P	Predictor	Beta	P
<u>Summary Variables</u>							
Avg Left Dominant (mean 22.5°, 157.5°/mean 45°, 135°)	1.01 (.35)	Marijuana	0.15	*	---	---	
	1.04 (.29)	Tobacco	0.003	*	Marijuana	---	*
		Alcohol	0.15	*			0.12
Avg Right Dominant (mean 67.5°, 112.5°/mean 45°, 135°)	1.06 (.35)	Tobacco	.003	*	---	---	
	1.00 (.40)	Marijuana	0.12	*	---	---	
<u>Asymmetrical Angles: Left Dominant</u>							
22.5° (22.5°/ mean 45°, 135°)							
157.5° (157.5°/ mean 45°, 135°)							
<u>Asymmetrical Angles: Right Dominant</u>							
67.5° (67.5°/ mean 45°, 135°)	1.16 (.39)	Tobacco	0.004	**	---	---	
	1.00 (.36)	Alcohol	0.24	**	---	---	
112.5° (112.5°/ mean 45°, 135°)							

*
p<.05,**
p<.01,***
p<.001