Published in final edited form as:
Alcohol Clin Exp Res. 2011 March ; 35(3): 431–442. doi:10.1111/j.1530-0277.2010.01360.x.

Number Processing in Adolescents with Prenatal Alcohol Exposure and ADHD: Differences in the Neurobehavioral Phenotype

Joseph L. Jacobson[1], **Neil C. Dodge**[1], **Matthew J. Burden**[1], **Rafael Klorman**[2], and **Sandra W. Jacobson**[1]

[1]Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, Michigan

[2]Department of Clinical and Social Sciences in Psychology, University of Rochester, Rochester, New York

Abstract

Background—Poor arithmetic performance is among the most sensitive outcomes associated with prenatal alcohol exposure and is also common in individuals with attention deficit hyperactivity disorder (ADHD). We hypothesized that prenatal alcohol exposure would be associated with deficits in the most fundamental aspects of number processing, representation of quantity and distance; whereas ADHD would be associated with deficits in calculation, the form of number processing most dependent on attention and memory.

Methods—262 inner-city, African American adolescents, who had been evaluated prospectively for prenatal alcohol exposure and ADHD, were assessed on a number processing test comprised of 7 subtests.

Results—More heavily alcohol-exposed adolescents were four times more likely to meet diagnostic criteria for ADHD than those whose mothers abstained from alcohol use during pregnancy. Two dimensions of number processing were identified in a factor analysis—magnitude comparison and calculation. As hypothesized, prenatal alcohol exposure was more strongly related to the former; ADHD, to the latter. Moreover, the relation of prenatal alcohol to calculation was fully mediated by magnitude comparison, whereas the relation of ADHD to calculation was mediated by IQ but not by magnitude comparison.

Conclusion—These data confirm findings from previous studies identifying arithmetic as a particularly sensitive developmental endpoint for prenatal alcohol exposure. Whereas difficulties with arithmetic in ADHD are mediated by domain-general deficits in overall cognitive ability, fetal alcohol-related arithmetic difficulties are mediated primarily by a specific deficit in the core quantity system involving the ability to mentally represent and manipulate number. These data suggest that different interventions are likely to be effective for remediating arithmetic problems in children with prenatal alcohol exposure than in non-exposed children with ADHD.

Keywords

Fetal alcohol spectrum disorder; prenatal alcohol exposure; arithmetic; number processing; magnitude comparison; attention deficit hyperactivity disorder

Corresponding Author: Joseph L. Jacobson, Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, 2751 E. Jefferson, Suite 460, Detroit, Michigan 48207, Tel: (313) 993-5454; Fax: (313) 993-3428, joseph.jacobson@wayne.edu.

Prenatal alcohol exposure is associated with a broad range of neurocognitive deficits, including IQ (Jacobson et al., 2004; Streissguth et al., 1990), attention and executive function (Burden et al., 2005a; Coles et al., 1997; Kodituwakku et al., 1995), verbal learning and memory (Mattson et al., 1996; Willford et al., 2004), and cognitive processing speed (Coles et al., 2002; Streissguth et al., 1990; S. Jacobson et al., 1993, 1994). Among the cognitive deficits seen in relation to prenatal alcohol exposure, arithmetic is a particularly sensitive endpoint (Rasmussen and Bisantz, 2009). In a large moderate-to-heavily exposed cohort, arithmetic was the domain of academic achievement most strongly related to maternal drinking in pregnancy at 7.5 years on the Wide Range Achievement Test (WRAT-R) (Streissguth et al., 1990) and at 14 years on the arithmetic subtest of the Wechsler Intelligence Scales for Children (WISC-R) (Streissguth et al., 1994). Similarly, in another moderate-to-heavily exposed cohort, arithmetic was the academic subtest of the Kaufman Assessment Battery for Children most strongly related to prenatal alcohol exposure at 6 years (Coles et al., 1991), and arithmetic and digit span were the WISC-III subtests most strongly related to pregnancy drinking in our moderate-to-heavily exposed Detroit cohort at 7.5 years (Jacobson et al., 2004).

In a study comparing adolescents with alcohol-related dysmorphic features with a group of adolescents in special education classes, the special education students were more impaired in basic reading and spelling, whereas the alcohol-exposed adolescents were more impaired in mathematics and mathematical reasoning (Howell et al., 2006). In a study of 6.5 year olds, low-to-moderate exposure was related to poorer performance on the WRAT-R tests of reading, spelling, and arithmetic, but only the effect on arithmetic was dose-dependent and remained significant after statistical adjustment for IQ (Goldschmidt et al., 1996). In a study of adolescents and adults diagnosed with fetal alcohol syndrome (FAS) or fetal alcohol effects, average academic functioning in arithmetic on the WRAT-R was at the second grade level (Streissguth, et al., 1991), and the arithmetic scores were significantly lower than the reading or spelling scores (Kerns et al., 1997).

The children in our Detroit cohort were administered reaction time tasks at 7.5 years using a Sternberg (1966) paradigm to assess four domains of cognitive processing—short-term memory scanning, mental rotation, directional discrimination, and number comparison (Burden et al., 2005b). In the Sternberg paradigm, the slope of the participant's reaction times across task items of increasing difficulty is used to assess cognitive processing speed and efficiency in a given domain. Measuring the slope makes it possible to assess the participant's efficiency in the domain in question, controlling for influences from other, unrelated domains required for performance of the task, including response organization and execution and motor speed. Prenatal alcohol exposure was related to poorer cognitive processing efficiency only on the number comparison task. Kopera-Frye et al., (1996) compared adults with FAS or fetal alcohol effects with healthy controls matched for age, gender, and education level on a series of number processing tasks. Although the performance of the alcohol-exposed adults on number reading and dictation was not affected, they performed significantly more poorly on tasks involving arithmetic calculation and proximity judgment.

Behaviorally many children with prenatal alcohol exposure exhibit problems of inattention and hyperactivity that resemble those seen in attention deficit hyperactivity disorder (ADHD) (Coles et al., 1991; Nanson and Hiscock, 1990; Steinhausen et al., 1993). ADHD is characterized by difficulties in sustaining attention and completing tasks, especially those requiring a higher degree of organizational skills or sustained mental effort. The clinical definition of ADHD cites inattention and/or hyperactivity-impulsivity as primary symptoms, with three proposed subtypes: predominantly inattentive, predominantly hyperactive-impulsive, and combined (DSM-IV, 1994). The prevalence of ADHD in a large population-

based, Minnesota birth cohort (n = 5718) using rigorous DSM diagnostic criteria was 9.4% (Barbaresi et al., 2002), which is comparable to prevalence rates in smaller studies in other U.S. cities (Jensen et al., 1999; Shekim et al., 1985). In a case-control study, children with ADHD were 2.5 times more likely to have been exposed prenatally to alcohol daily or during maternal binge drinking episodes, compared with children not diagnosed with ADHD (Mick et al., 2002). In another study, psychiatric interviews were used to assess a sample of clinic-referred children who were heavily exposed to alcohol prenatally and a comparison group matched for age, socioeconomic status, race, and gender (Fryer et al., 2007). More than 90% of the alcohol-exposed children met DSM-IV diagnostic criteria for ADHD, compared with 30.0% of the comparison group, many of whom were also clinic referred. Because children with disruptive behavior problems, such as ADHD, are over-represented in clinic-referred samples, these proportions probably overstate the prevalence of ADHD symptomatology in children with prenatal alcohol exposure. Nevertheless, it is significant that ADHD was by far the most prevalent DSM-IV diagnosis in the alcohol-exposed group in the Fryer et al. study (see also Aronson et al., 1997).

Although many children with prenatal alcohol exposure meet behavioral criteria for a diagnosis of ADHD, the underlying cognitive and neurophysiological bases of these disorders may be distinct.Coles et al. (1997) administered a series of neuropsychological tests to a group of prospectively-ascertained, moderate-to-heavily exposed children and children from a clinic-referred ADHD group. They found poorer sustained and focused attention in the ADHD group, whereas the alcohol-exposed children exhibited more problems in working memory and cognitive flexibility (but cf. Vaurio et al., 2008). In one recent study, both alcohol exposure and ADHD were associated with poorer adaptive behavior (communication, daily living skills, socialization) assessed on the Vineland Adaptive Behavior Scale, but socialization problems increased with age in the alcohol-exposed children, possibly due to the increasing importance of cognitive flexibility for adaptive behavior as the child matures (Crocker et al., 2009). We have recently identified a unique pattern of EEG event-related potential (ERP) response in a Go/No-go task in young adults with a history of childhood ADHD but no prenatal alcohol exposure (“idiopathic” ADHD) (Burden et al., 2010). This unique response pattern was not seen in young adults with a history of both ADHD and prenatal alcohol exposure or with alcohol exposure and no ADHD, indicating differences at the neural processing level in participants with ADHD with and without a history of prenatal alcohol exposure. Moreover, it is noteworthy that children with ADHD symptoms who also have a history of prenatal alcohol exposure often show a poorer clinical response to psychostimulant treatment than children with idiopathic ADHD (O’Malley et al., 2000). Taken together, these findings suggest that, although children with prenatal alcohol exposure often display overt behavioral characteristics of ADHD, the cognitive and neurophysiological bases of their ADHD symptomatology may differ from that of children with idiopathic ADHD.

Brain lesion and neuroimaging studies have identified two distinct functional neural networks relating to number processing—(a) a core quantity system, in which numerical quantity (magnitude and distance) is represented in a language-independent format, possibly resembling a number line (Dehaene et al., 2004); and (b) mental calculation, involving manipulation of verbally-encoded numbers and verbally-stored knowledge (e.g., arithmetic facts) (Menon et al., 2000; Zago et al., 2001). Magnitude comparison, the ability to evaluate relative quantities, has been shown to be mediated primarily by activity in the anterior portion of the horizontal section of the intraparietal sulcus (HIPS) (Dehaene et al., 2003; Eger et al., 2003; Pinel et al., 2004). It emerges early in development (Meintjes et al., 2010; Wynn et al., 2002) and is clearly evident at 4–5 years of age (Cantlon et al., 2006; Temple and Posner, 1998). The anterior HIPS is activated by the representation of semantic information about magnitude, whether presented as Arabic numbers, sequences of words, or

analogically (e.g., by numbers of dots) (Dehaene and Cohen, 1995; Naccache and Dehaene, 2001). Calculation involves recruitment of a fronto-parietal number processing network that includes the anterior HIPS (Chochon et al., 1999; Simon et al., 2002) and other parietal areas, such as the angular gyrus, in interaction with an executive brain system (Zago et al., 2008) not specific to number processing. The executive brain system mediates the integration and management of numerical operations in working memory, response decision and execution, and error monitoring (Gruber et al., 2001, Menon, 2000).

While number processing is a particularly sensitive endpoint for fetal alcohol exposure, many children with ADHD also perform poorly in arithmetic. This finding is generally attributed to ADHD-related deficits in attention and executive function, including difficulties in retrieval of numerical information from semantic memory, allocation of attention, inhibition of retrieval of irrelevant associations, and attention to detail (Benedetto-Nasho and Tannock, 1999; Lindsay et al., 1999). The notion that the arithmetic difficulties associated with ADHD are related to attention problems rather than a deficit in the ability to represent and manipulate quantity is further supported by findings that psychostimulant treatments can ameliorate arithmetic performance in children with ADHD (Benedetto-Nasho and Tannock, 1999; Carlson et al., 1991) but not in children with severe dyscalculia. (Rubinsten et al., 2008).

In this study, we administered a number processing test adapted from Kopera-Frye et al. (1996) in collaboration with S. Dehaene to adolescents participating in the 14-year follow-up assessment of our Detroit longitudinal cohort. This test includes subtests that assess exact calculation, numeric approximation, and magnitude comparison. Based on the data suggesting that arithmetic is particularly sensitive to prenatal alcohol exposure, we hypothesized that alcohol exposure would be associated with deficits in fundamental aspects of number processing—representation of quantity and distance, which are assessed in the magnitude comparison subtests. Given that magnitude comparison is a critical component of arithmetic calculation (Dehaene, 1997), we further hypothesized that a deficit in magnitude comparison might account for (mediate) fetal alcohol-related deficits in exact calculation. Conversely, given that deficits in arithmetic in ADHD appear to reflect domain-general problems in attention and executive function, we hypothesized that ADHD would be associated primarily with deficits in exact calculation, the form of number processing most dependent on higher-order cognitive function. Because IQ provides a measure of overall intellectual function, we hypothesized that ADHD-related deficits in IQ would mediate observed impairment in exact calculation but that IQ would not mediate the predicted fetal-alcohol related deficits in magnitude comparison.

Methods

Participants

The Detroit longitudinal cohort was recruited prospectively during pregnancy between September 1986 and April 1989 to assess the effects of moderate-to-heavy levels of prenatal alcohol exposure (J. Jacobson et al., 1993). All African American gravidas were screened for alcohol consumption during their first visit to a prenatal clinic in a large urban maternity hospital. Only African American women were recruited because they constituted 92% of the women delivering at this facility. All women who averaged at least 7 drinks/ week (0.5 oz absolute alcohol (AA)/day) at the time of conception were invited to participate in the study. Approximately 5% of the lower level drinkers and abstainers were also invited to participate; recruitment of the latter was adjusted periodically to balance the number of infants whose mothers drank at moderate-to-heavy levels at conception with an equal number of infants whose mothers abstained or drank at lower levels. Due to the prevalence of cocaine use in this population during the period when recruitment took place, we sought

to minimize potential confounding of prenatal alcohol and cocaine exposure. Given that all cocaine-using heavy drinkers were included by definition in the study design, we also recruited a group of heavy cocaine (≥2 days/week), light alcohol (<7 drinks/week) users, which reduced the confounding of these exposures from $r = .42$ to .19 (Jacobson and Jacobson, 1996). Although recruitment was stratified by maternal drinking during pregnancy, the data presented here have been analyzed in terms of continuous measures of prenatal alcohol exposure rather than discrete groups. Infant exclusionary criteria were birth weight <1500g, gestational age <32 weeks, major chromosomal anomalies or neural tube defects, and multiple births.

The children were evaluated at 6.5, 12, and 13 months (J. Jacobson et al., 1993; S. Jacobson et al., 1993, 1994) and 7.5 years (Burden et al., 2005a; Jacobson et al., 2004). At 14 years, 293 adolescents (61.0% of the original cohort) were assessed.1 This paper presents data for the 262 adolescents who were assessed on the number processing test described below. Sixteen adolescents were not tested on number processing at the beginning of the study because the test was still under development; 1 adolescent, who found the practice problems difficult, refused to do the test; 2 adolescents left the laboratory early before the test was scheduled to be administered; and data were not recorded for 12 adolescents due to a technical problem with the computer program. Informed consent was obtained from the mothers at recruitment and each laboratory visit; written assent was obtained from the adolescents at 14 years. Approval for human research was obtained from the Wayne State University Human Investigation Committee. Each adolescent received lunch and a gift, and the mother received a small remuneration.

Procedure

Assessment of prenatal alcohol exposure—Maternal alcohol consumption during pregnancy was assessed using a timeline follow-back approach to determine incidence and amount of drinking (Jacobson et al., 2002a; Sokol et al., 1985). At each prenatal clinic visit ($M = 5.2$ vists, SD = 3.4), the mother was questioned about how much alcohol she had consumed during the past 2 weeks, with recall linked to certain times of day and activities. Volume was recorded for each type of beverage consumed each day, converted to AA using multipliers proposed byBowman et al. (1975) (liquor, 0.4; beer, 0.04; wine, 0.2; wine coolers, 0.05), and averaged across the clinic visits to provide a contemporaneous report of ounces of AA/day during pregnancy. Each ounce of AA is equivalent to two standard drinks. At the first visit, the mother was also asked to recall her day-by-day drinking during a typical week around the time she became pregnant, i.e., at conception. Smoking during pregnancy was reported at the first antenatal visit in terms of mean number of cigarettes per day. Detailed drug use data were obtained at each clinic visit except the first. Because of wide variability in the dosage and degree of purity of illicit drugs, prenatal exposure to cocaine and marijuana was summarized in terms of average number of days per month (see Jacobson et al., 2004).

14-year assessment—Each participant was administered the Wechsler (1992) Intelligence Scales for Children, 3rd edition (WISC-III) and a battery of neuropsychological tests. The test battery was administered over a 3-year period by six highly trained research assistants, five of whom were Master's level students in psychology. The sixth tester has a B.S. in psychology and 20 years of neuropsychological testing experience in our laboratory.

[1]Three children in the cohort had died, 6.0% of the families had moved out of state, 5.8% declined to participate at 14 years, and 26.5% could not be located. The mothers of the children who participated at 14 years were older than those lost to follow-up (27.0 vs. 25.3 years, respectively, $t(478) = 3.13$, $p < .01$) and tended to drink slightly more around the time of conception (0.96 vs. 0.65 oz AA/day, respectively, $t(478) = 1.83$, $p < .07$) but did not differ in alcohol, cocaine use, or smoking during pregnancy, years of education, or socioeconomic status, nor did the children differ in gender or 7.5-year IQ (all p 's > .10).

There were no systematic between-examiner differences in the participants' test scores; for IQ, examiner $F(5, 261) = 1.78$, $p > .10$.

We adapted and programmed a number processing test designed by S. Dehaene (Kopera-Frye et al., 1996) for administration on a desktop computer. Our new version contained seven 32-problem subtests. In exact addition, exact subtraction, and exact multiplication, an equation was presented on the screen (e.g., 2 + 5 = ?), and the participant entered his/her answer on the computer keypad. In approximate addition and approximate subtraction, an equation was presented at the top of the screen with two choices displayed below it, and the participant used the computer mouse to select which of the two choices was closest to the correct answer. In proximity judgment, one number appeared at the top of the screen with two below it, and the participant used the mouse to select which of the two numbers was closest to the number displayed at the top. In number comparison, two numbers were displayed on the screen, and the participant used the mouse to indicate which was larger. The examiner provided instructions for each of the subtests orally. Each subtest was preceded by a 10-item practice round, which was terminated once the participant provided three correct answers in a row. All participants demonstrated an understanding of the instructions during the practice rounds, with the exception of one adolescent whose data were excluded as noted above. The participant could take as long as necessary to respond to each problem and received no feedback regarding the accuracy of his/her responses.

Each participant was also administered the Wechsler Individual Achievement Test (WIAT) for Mathematical Reasoning (Wechsler, 1992). DSM-IV (1994) defines a learning disorder as performance on a standardized achievement test substantially below the participant's IQ score. "Substantially below" is usually defined as a discrepancy of more than 2 standard deviations; however, for socioeconomically disadvantaged groups who perform more poorly on IQ tests, a discrepancy between 1 and 2 standard deviations is recommended. Following this recommendation, we defined mathematics disorder as a WIAT Mathematical Reasoning standard score more than 1.5 standard deviations below the participant's IQ score.

Executive function was assessed on the Wisconsin Card Sorting Test (WCST; Berg, 1948), the Delis-Kaplan version of the Stroop Color-Word Test (Delis et al., 2001), and the Controlled Oral Association Test (COWAT; Spreen and Strauss, 1991). The WCST assesses the ability to use feedback to alter one's response when the criterion for the correct response changes ("set shifting") and the ability to inhibit a previously learned but now inappropriate response. The Delis-Kaplan version of the Stroop has several conditions. In the "color naming" condition, the participant is shown a page with 100 patches of color, which s/he is asked to name as quickly as possible. In the "interference" condition, in which color names are printed in a different-colored ink (e.g., "red" printed in green ink), the participant is asked to name the colors of the printed words, which requires him/her to overcome an automatic response to read the printed word. In the "switch" condition, some words on the page are surrounded by a box, and the participant is asked to read the word aloud if it is surrounded by a box but to name the ink color if it is not. In the COWAT, a test of verbal fluency, the participant is asked to list as many items beginning with a given letter as possible within 60 s. An executive function composite score was constructed by averaging standard scores for five outcomes—number of categories completed and perseverative errors on the WCST, time to complete the interference and switch conditions on the Stroop, and number of words listed on the COWAT.

ADHD diagnosis—At 7.5 years, the child was rated by his/her primary caregiver, classroom teacher, and study examiner on a check list of behavioral symptoms that provide the basis for a DSM diagnosis of ADHD, using the Barkley-DuPaul ADHD Rating Scale (Barkley, 1990). At 14 years, the participant was rated again on these symptoms by the

primary caregiver, classroom teacher, and study examiner, using the Disruptive Behavior Disorders Scale (DBD: Pelham et al., 1992). Internal consistency reliability for ADHD rating scales is high; for the DBD, in a sample of 1505 children rated by 990 teachers, Cronbach's α was .95 (Pelham et al., 1992). Teacher ratings were provided for 69.1% of the 262 children in this sample at 7.5 years; 65.3% at 14 years. Examiner ratings were provided by the research assistant who had administered the neuropsychological battery to the participant and worked closely with him/her on a one-on-one basis during 4–5 hr of testing. Symptom counts were computed separately for inattention and hyperactivity at each age by totaling how many of the nine DSM-IV behavioral criteria for each ADHD subtype were endorsed as "often" or "very often" by parent, teacher, or examiner. Participants were assigned an ADHD diagnosis following procedures developed in collaboration with R. Klorman and J. Nigg, two licensed clinicians who are widely recognized for their expertise in ADHD research. An ADHD classification was assigned if (a) at least 6 of the 9 symptoms for inattention and/or 6 of the 9 symptoms for hyperactivity/impulsivity were endorsed ("pretty much" or "very much" true of child) by one or more informants at either 7.5 or 14 years, (b) some impairment (≥ 2 ADHD symptoms) was reported in two or more settings (operationally defined in terms of reports from at least two informants—parent, teacher, examiner), and (c) some impairment (≥ 2 symptoms) was documented at 7.5 years. Six children who met criteria for ADHD at 14 years were not seen at 7.5 years. In four of these cases, mothers retrospectively reported the presence of at least two ADHD symptoms in early childhood. In the other two cases, the mother was not interviewed retrospectively, and confirmation of symptoms at 7.5 years is not available.

Data Analysis

Variable transformations—Maternal drinking during pregnancy (average oz AA/day), which was positively skewed, was subjected to log $x + 1$ transformation to reduce the influence of extreme outliers. Pregnancy smoking for six mothers, whose values for daily cigarette intake were more than 3 standard deviations above the sample mean, was recoded to 1 point greater than the highest observed value within 3 standard deviations of the mean as recommended by Winer (1971). Although the distributions of the number processing subtest scores were negatively skewed, these distributions were generally continuous. For those subtests on which a gap of 3 or more points separated a few very low scores from the rest of the distribution, the scores below that gap were recoded to one point less than the lowest score falling within the continuous distribution to reduce the influence of the lowest scores on the correlations. The number of outliers whose scores were recoded using this procedure ranged from 0 for exact subtraction and proximity judgment to 6 for exact addition.

Control variables—Twelve control variables were assessed as potential confounders of the relation of prenatal alcohol exposure and ADHD to number processing performance: participant age at testing; gender; mother's age at delivery; maternal smoking (cigarettes/day), cocaine (at least once/week—yes/no), and marijuana (days/month) use during pregnancy; primary caregiver's socioeconomic status (SES) based in the Hollingshead (1975) scale, years of education, and verbal competence (Peabody Picture Vocabulary Test-Revised); and self-reported adolescent alcohol, smoking, and marijuana use (yes/no). SES and maternal years of education were assessed at the 14-year visit; the Peabody data were obtained at the 6.5-month infant visit and at a later visit from those who did not become the child's primary caregiver until a later age.

Factor analysis—The degree to which the seven subtests reflect distinct aspects of number processing was examined in a principal components analysis with varimax rotation, which yielded two factors. Composite scores were derived by averaging the scores of the

subtests that loaded most strongly on each of these factors. One composite, calculation, was comprised of the five exact and approximate calculation subtests; the other, magnitude comparison, was comprised of number comparison and proximity judgment.

Regression analysis—The number processing subtest and composite scores were each examined in two sets of regression analyses—one in relation to prenatal alcohol exposure (log AA/day during pregnancy); the other in relation to ADHD (present/absent). Regression was used to control for confounding. Based on a Monte Carlo simulation study, Maldonado and Greenland (1993) concluded that the inclusion of all control variables related to a given outcome at $p < .20$ is effective in protecting against confounding. They noted, however, that the inclusion of a large number of control variables that only minimally confound the relation of exposure to a given outcome could result in a loss of precision. Greenland and Rothman (1998) have recommended a "change-in-estimate" approach that controls for all potential confounders, whose inclusion alters the relation of exposure to outcome by at least 10%. Given these considerations, we used a two-tier strategy to determine the inclusion of confounding variables in the multiple regression analyses. All control variables that were related to an endpoint at $p < .20$ were considered for inclusion in the analyses examining effects on that endpoint. Two regressions were run for each endpoint—one in which prenatal alcohol exposure was entered at the first step; the other in which ADHD was entered first. The control variables were then entered hierarchically in each regression using a forward selection approach, with order of entry determined by the strength of the correlation of the control variable to the endpoint in question. Control variables were retained if their entry into the model altered the regression coefficient for alcohol exposure or ADHD by at least 10% at the step at which they were entered. Because the adolescent alcohol, smoking, and marijuana measures were not available for all participants, they were examined in separate regression analyses. The assumptions of regression (e.g., linearity, heteroscedasticity) were met, although the distributions of the number processing subtests were moderately skewed (Median = −1.98) due to good performance by a large proportion of the children.

Each regression analysis was re-run adding the participant's IQ score at the last step to determine whether IQ mediates the relation of alcohol exposure or ADHD to the outcome in question. Mediation was inferred when the addition of IQ reduced the magnitude of the standardized regression coefficient for alcohol exposure or ADHD and was tested statistically using the Sobel (1982) method, which assesses whether the product of the regression coefficients relating independent variable to mediator and mediator to dependent variable differs significantly from zero. The hypothesis that the effects of prenatal alcohol and ADHD on calculation might be mediated by magnitude comparison was also tested using the Sobel method. Partial mediation was inferred if the direct effect of prenatal exposure or ADHD on calculation remained significant when the indirect effect mediated through magnitude comparison was included in the model. Full mediation was inferred if the direct effect of prenatal exposure or ADHD on calculation was decreased essentially to zero when magnitude comparison was included in the model.

Results

Sample Characteristics

The sample characteristics are summarized in Table 1. The sample is economically disadvantaged and poorly educated. Almost half (49.6%) of the families are in Levels IV or V of the Hollingshead SES scale (semi-skilled or unskilled workers), and only 53.8% of the primary caregivers completed at least 12 years of education. Eighty-two per cent of the mothers had reported using alcohol during pregnancy, 62.2% smoked, 21.0% used cocaine, and 30.1% used marijuana. A majority of the participants were exposed to moderate levels

of alcohol during gestation; only 6.9% of the mothers drank heavily during pregnancy (see Table 2). Adolescent alcohol, smoking, and drug use is still relatively rare at this age: 87.0% of the adolescents report no alcohol use, although 2.9% report drinking weekly, with the heaviest drinker reporting 21 drinks per month. Few of the participants (only 3.8%) report smoking; 1.4% smoke 1–5 cigarettes per week; the others, ¼ to 1 pack/day. Six percent report marijuana use; a majority of those (3.7%), less than once/week. None of the participants report using cocaine, opiates, or other illicit drugs.

IQ scores are in the range of those commonly found in inner-city, African American samples (Sattler, 1992); the WIAT math scores are slightly higher than the IQ scores on the average (Table 1). Only one of the participants meets criteria for a diagnosis of mathematics disorder. ADHD is significantly more prevalent in participants with prenatal alcohol exposure (Table 2). Whereas 10.9% of the participants whose mothers abstained from alcohol during pregnancy meet criteria for ADHD, a rate similar to other populations (Barbaresi et al., 2002), 44.4% of the participants born to heavy drinking (≥ 1.0 oz AA/day) women qualify for this diagnosis.

Factor Analysis

Table 3 presents the results of a factor analysis of the seven number processing subtests. The two factors that emerged jointly explain 71.6% of the variance. The exact and approximate calculation subtests all load strongly on the first factor. Although some individuals may solve numerical approximation problems quickly without calculation, these data suggest that many of the participants solved the approximation problems by first performing the calculation and then determining which of the choices provided in the test was closest to the answer they had calculated. By contrast, the two subtests involving magnitude comparison —number comparison and proximity judgment—load on a separate factor, which is consistent with findings from previous studies that mental calculation and magnitude comparison are functionally distinct aspects of number processing (e.g., Menon et al., 2000; Stanescu-Cossin et al. 2000). Scores on the three exact and two approximate calculation subtests were averaged to provide a composite measure of calculation. Scores on the number comparison and proximity judgment subtests provided a composite measure of magnitude comparison.

Relation of ADHD and Prenatal Alcohol Exposure to Number Processing

Both ADHD and prenatal alcohol exposure are associated with poorer performance on the WIAT mathematics achievement test, r's = −.21, $p < .001$, and −.12, $p < .05$, respectively. ADHD is significantly related to all seven number processing subtests, after control for confounders, but the associations are markedly stronger with the exact and approximate calculation subtests than with number comparison or proximity judgment (Table 4). By contrast, prenatal alcohol exposure is significantly related to only one calculation subtest—approximate subtraction—and is most strongly related to number comparison and proximity judgment. This pattern is also seen on the composite measures derived from the factor analysis. Although ADHD and prenatal alcohol exposure are significantly related to both composite measures, ADHD is more strongly related to calculation, whereas prenatal alcohol is related most strongly to magnitude comparison. The potential confounders included in the final model for each regression analysis are shown in the footnotes to Table 4. To avoid listwise deletion, adolescent alcohol, smoking, and marijuana were examined in separate analyses. Current adolescent smoking and marijuana do not qualify as potential confounders of effects on any of the number processing endpoints (all p's > .20). Current adolescent alcohol is related at $p < .20$ to two endpoints—exact subtraction and approximate addition—but its inclusion in the final models does not reduce the standardized regression coefficients for either ADHD or prenatal alcohol exposure.

The regression analyses in Table 4 examining effects of prenatal exposure include all the children in the sample, regardless of whether or not they met criteria for ADHD. Similarly, the analyses examining effects of ADHD include all children regardless of their degree of prenatal exposure to alcohol. Multiple regression analyses of each of the number processing composite scores, in which prenatal alcohol and ADHD were entered simultaneously, make clear that each of these predictors is independently associated with poorer number processing (Table 5). Thus, although ADHD is more prevalent in the more heavily exposed children, the effects of each of these predictors on number processing are independent.

Mediation of the effects of ADHD and prenatal alcohol on number processing by IQ

As predicted, the relation of ADHD to the exact and approximate calculation subtests is markedly reduced when IQ is added at the last step of the multiple regression analysis (Table 4). This mediation by IQ suggests that effects of ADHD on aspects of calculation not specific to the representation of number, such as, attention and executive function, mediate the poorer number processing seen in ADHD. The hypothesis that IQ mediates the effect of ADHD on the two composite measures was evaluated statistically using the Sobel test. The relation of ADHD to both composites is significantly mediated by IQ; for calculation, $z = -2.75$, $p < .01$, for magnitude comparison, $z = -1.96$, $p < .05$. By contrast, IQ does not mediate the effect of prenatal alcohol exposure on either calculation, $z = -1.37$, or magnitude comparison, $z = -1.28$, both p's > .15.

The hypothesis that executive function is an important aspect of the deficit in overall cognitive ability that mediates the effect of ADHD on calculation was examined in a multiple regression analysis, in which ADHD, IQ, and our composite measure of executive function were entered hierarchically. As shown in Table 4, the entry of IQ reduces the association of ADHD to calculation from β = −.34 to −.24. The addition of executive function further reduces the effect of ADHD to β = −.19 and reduces the effect of IQ on calculation from β = .37 to .27. These data indicate that executive function is an important component of the deficit in overall intellectual function that mediates the effect of ADHD on calculation. When the influence of executive function on number processing is examined in regression analyses that do not include IQ, the data suggest a possible small role in mediating the relation of prenatal alcohol exposure to magnitude comparison, reducing the correlation from −.23 to β = −.20. By contrast, it plays a much more substantial role in mediating the effect of ADHD on calculation, reducing the correlation from −.34 to β = −.17.

Mediation of the effects on calculation by magnitude comparison

The hypothesis that magnitude comparison mediates the effect of prenatal alcohol exposure on exact and approximate calculation was tested in the path model shown in Figure 1a. The path relating prenatal alcohol exposure to calculation via magnitude comparison is significant, Sobel test $z = -3.54$, $p < .001$. Partial vs. full mediation was assessed by examining the direct effect of prenatal alcohol on calculation after controlling for magnitude comparison and gender (the potential confounder in the regression model in Table 4). A comparison of the regression analysis relating prenatal alcohol to calculation (Table 4) with the path model (Fig. 1a) shows that, when magnitude comparison is added to the model, the regression coefficient for prenatal alcohol exposure is decreased from −.14 to −.02, indicating that the effect of prenatal alcohol on calculation is fully mediated by its effect on magnitude comparison.

The hypothesis that magnitude comparison mediates the effect of ADHD on calculation was tested in the path model shown in Figure 1b. The path relating ADHD to calculation via magnitude comparison is significant, Sobel test $z = -3.72$, $p < .001$. By contrast to prenatal

alcohol exposure, however, the effect of ADHD on calculation is only partially mediated by magnitude comparison. When magnitude comparison is added to the model relating ADHD to calculation, the regression coefficient for ADHD decreases from −.34 (Table 4) to −.22 (Fig. 1b) but remains highly significant. When IQ is added to the model (Fig. 1c), the unique variance explained by the direct effect of ADHD is further reduced to −.16.

Discussion

This study confirms previous reports that a large proportion of children with prenatal alcohol exposure exhibit the inattention and/or hyperactivity that are characteristic of ADHD. Participants exposed *in utero* to at least 1 oz AA/day on average were four times more likely to meet diagnostic criteria for ADHD, compared with those whose mothers abstained during pregnancy. Although it seems likely that this increase in ADHD behavioral symptoms is a direct consequence of fetal alcohol exposure, it could also be influenced by possible genetic differences in the prevalence of ADHD behaviors in families who use alcohol in pregnancy. Data fromColes et al. (1997), Burden et al. (2010), and others suggest that, despite similarities in the behavioral characteristics assessed on parent and teacher ADHD rating scales, a detailed examination of the cognitive and neurophysiological features of prenatal alcohol exposure and ADHD reveals important differences. Although poorer number processing is seen in both these disorders, we found differences in the aspects of number processing that are affected. The principal deficits seen in prenatal alcohol exposure relate to the core quantity system, which involves the processing of relative magnitude (i.e., number comparison and proximity judgment). By contrast, in ADHD the principal deficits are seen in exact and approximate calculation, which depend heavily on domain-general aspects of attention and memory not specific to number processing.Zago et al. (2008) characterize these nonspecific aspects of arithmetic as an executive brain system that mediates the integration and management of numerical operations in working memory, response decision and execution, and error monitoring—domains of cognitive processing that are strongly reflected in IQ scores. The hypothesis that poorer function of the executive brain system plays an important role in the deficits in number processing seen in ADHD is supported by our finding that the relation of ADHD to number processing is significantly mediated by IQ and executive function. By contrast, IQ does not mediate the effects of prenatal alcohol exposure on either calculation or magnitude comparison.

Because the mental representation of relative quantities assessed in the magnitude comparison subtests is an essential element of calculation (Geary, 1993), it is not surprising that magnitude comparison mediates the effects of both prenatal alcohol exposure and ADHD on calculation. What is striking, however, is that the relation of prenatal alcohol to calculation is fully mediated by magnitude comparison; once this aspect of number processing is entered in the model, prenatal alcohol is no longer related to calculation. The alcohol-related deficit in this core element of number processing may explain why arithmetic has been found to be particularly sensitive to prenatal alcohol exposure in so many studies. We note that exact subtraction was the calculation subtest most strongly related to prenatal alcohol exposure, which is consistent with the observation that subtraction is the arithmetic operation that is most heavily dependent on magnitude comparison (Chochon et al., 1999; Ischebeck et al., 2006). By contrast, the relation of ADHD to calculation was only partially mediated by magnitude comparison; much of the effect of ADHD was mediated by domain-general cognitive competence measured by IQ.

The findings reported here are consistent with the evidence of fetal alcohol-related number processing deficits reported elsewhere (e.g., Goldschmidt et al., 1996; Howell et al., 2006; Streissguth et al., 1994) and with data from our Cape Town, South Africa, cohort linking fetal alcohol exposure to poorer numerosity in infancy (Jacobson et al., 2002b) and poorer

magnitude comparison and number recognition at age 5 years (Dodge et al., 2007). The specific fetal alcohol-related deficit in magnitude comparison identified in this study is consistent with evidence from magnetic resonance imaging (MRI) studies reporting alcohol-related structural deficits in the parietal region, which is known to play a major role in the core quantity system (Dehaene et al., 2003), and with evidence from a recent functional MRI (fMRI) study that we conducted in Cape Town (Meintjes et al., in press). Disproportionate size reductions in the parietal lobe have been reported in fetal alcohol-exposed children and adults (Archibald et al., 2001), and gray matter, cortical thickness, and shape anomalies have been reported in the parietal and temporal lobes of alcohol-exposed individuals (Sowell et al., 2001, 2002, 2008).

In Cape Town we used fMRI to study proximity judgment and exact addition in a sample of 10-year-old children diagnosed with FAS or partial FAS and matched controls (Meintjes et al., in press). The non-exposed control children activated the same fronto-parietal network that has been found to be specialized for number processing in studies of healthy children and adults (Chochon et al., 1999; Davis et al., 2009a; Pesenti et al., 2000). By contrast, the alcohol-exposed children activated much more widely distributed neural networks while performing these tasks—a broader range of frontal areas on both tasks, additional parietal pathways on the proximity judgment task, and on exact addition, a large cerebellar region that is activated only in particularly challenging calculation problems in adults (Kaufman et al., 2006; Menon et al., 2000). The widely distributed networks recruited by the alcohol-exposed children to perform these relatively simple number processing tasks suggest that these children may need to compensate for damage to fronto-parietal areas that normally mediate number processing (Fryer et al., 2007; Halperin and Schultz, 2006) and for a fetal alcohol-related deficit in the functional integration of the neural circuitry that supports efficient brain function in number processing.

Consistent with our findings in the present study, most researchers have attributed arithmetic problems in children with ADHD to impairments in attention, working memory, and executive function required for calculation (Benedetto-Nasho and Tannock, 1999; Lindsay et al., 1999). By contrast, children with developmental dyscalculia—the European equivalent of mathematics disorder in the DSM-IV—exhibit deficits in core numerical abilities; that is, the ability to understand and manipulate quantity.Rubinsten et al. (2008) found that arithmetic performance was ameliorated by administration of methylphenidate in children with ADHD who have difficulty with arithmetic but not in those with co-morbid developmental dyscalculia. Given that methylphenidate is known to enhance general cognitive functions, such as attention, spatial memory, motivation, and effortful processing, these data are consistent with the inference in the present study that the number processing impairment usually seen in ADHD is mediated by impairment in neural networks subserving general cognitive and executive function. By contrast, our data suggest that prenatal alcohol exposure is associated with a specific impairment in the ability to understand and manipulate quantity that does not appear to respond to methylphenidate.

Davis et al. (2009b) recently reported findings from an fMRI study of exact and approximate calculation comparing children with mathematical calculation difficulties with normally developing controls. Most of the group differences in brain activation were seen in frontal and basal ganglia regions known to mediate domain-general cognitive resources rather than the parietal areas. By contrast, two studies of children with developmental dyscalculia found reduced activations in the intraparietal sulcus, a region that is specialized for number processing (Kucian et al., 2006; Price et al., 2007). The deficit in the domain-general aspects of number processing seen by Davis et al. in children with mathematical calculation difficulties resembles that seen in the adolescents with ADHD in the present study, whereas the magnitude comparison deficits seen in our alcohol-exposed adolescents resemble the

deficits reported in children with dyscalculia. It should be emphasized, however, that only one of our study participants met diagnostic criteria for mathematics disorder, the DSM-IV equivalent of developmental dyscalculia. Although that individual was exposed to alcohol during gestation, his mother drank at very low levels (M = .06 oz AA/day). Thus, in our sample of adolescents exposed at moderate-to-heavy levels, prenatal alcohol appears to be associated with a specific deficit in magnitude comparison in individuals whose arithmetic achievement test scores fall within the normal range. Based on prior studies of arithmetic in patients with FAS (e.g., Kerns et al., 1997), a more severe magnitude comparison deficit would be expected in individuals exposed at higher levels.

One limitation of this study is that all participants are from a single ethnic group. However, because the number processing deficits seen in this sample in relation to prenatal alcohol exposure and ADHD have also been reported in studies with several different ethnic groups, these findings likely generalize to other populations as well. Although alcohol consumption is often difficult to recall accurately, one strength of this study is that maternal drinking during pregnancy was ascertained prospectively using a well-validated timeline follow-back approach (Jacobson et al., 2002a; Sokol et al., 1985), in which accuracy is facilitated by asking the respondent to recall specific days and contexts within which drinking occurred. Because ADHD was also ascertained prospectively, the sample is more representative of the larger population than in studies that are limited to clinic-referred patients, who are more likely to be behaviorally oppositional than non-referred children. Based on our prospective data, the prevalence of alcohol-exposed children meeting diagnostic criteria for ADHD, although elevated, is substantially lower than the 90%+ reported in studies of clinic-referred patients (e.g., Fryer et al., 2007). Although it is not possible to measure all of the potential confounders of the relation between prenatal alcohol exposure and number processing, our analyses of the influence of the control variables on the regression analyses indicate that the effects of prenatal alcohol and ADHD on exact subtraction, number comparison, and proximity judgment are not attributable to maternal smoking, cocaine, or marijuana use during pregnancy, maternal age at delivery, SES, the educational attainment or verbal competence of the primary caregiver, or the participant's gender, age at testing, or current use of alcohol, cigarettes, or marijuana.

Conclusions

These data confirm findings from previous studies indicating that arithmetic is a particularly sensitive developmental endpoint for prenatal alcohol exposure and implicate a specific aspect of number processing—magnitude comparison—as a core deficit associated with this exposure. Although difficulties with arithmetic are seen in both prenatal alcohol exposure and ADHD, different aspects of number processing are affected. Whereas arithmetic difficulties in ADHD are related to domain-general deficits in attention and executive function, in fetal alcohol exposure these difficulties appear to be attributable primarily to a specific deficit in the core number system involving the ability to mentally represent and manipulate relative quantities. Given this distinction, our data suggest that interventions that are effective for remediating arithmetic problems in children with ADHD—both pharmacological and behavioral—are unlikely to be effective in children with prenatal alcohol exposure and that interventions focusing on basic concepts relating to quantity and distance warrant particular consideration in remedial work with fetal alcohol-exposed children.

Acknowledgments

We thank Robert J. Sokol, Joel Ager, and Susan Martier, for their collaboration in the recruitment of the Detroit Prenatal Alcohol Exposure Cohort; Stanislas Dehaene, for his collaboration in the development of the computer-

based number processing test; Joel Nigg, for his consultation on the ADHD diagnostic procedures; Leslie Lundahl, for her contribution to the diagnosis of the participants; Renee Sun, Audrey Morrison, and Chie Yumoto, for their work in data collection; Douglas Fuller, for data management; and the adolescents and their mothers for their participation in the study. This study was funded by grants from the National Institute on Alcohol Abuse and Alcoholism (R01-AA06966, R01-AA09524, and P50-AA0706) and the Joseph Young, Sr., Fund from the State of Michigan.

References

Archibald SL, Fennema-Notestine C, Gamst A, Riley EP, Mattson SN, Jernigan TJ. Brain dysmorphology in individuals with severe prenatal alcohol exposure. Dev Med Child Neurol. 2001; 43:148–154. [PubMed: 11263683]

Aronson M, Hagberg B, Gillberg C. Attention deficits and autistic spectrum problems in children exposed to alcohol during gestation: A follow-up study. Dev Med Child Neurol. 1997; 39:583–587. [PubMed: 9344050]

Barbaresi WJ, Katusic SK, Colligan RC, Pankratz VS, Weaver AL, Weber KJ, Mrazek DA, Jacobsen SJ. How common is attention-deficit/hyperactivity disorder? Incidence in a population-based birth cohort in Rochester, Minn. Arch Pediatri Adolescent Med. 2002; 156:217–224.

Barkley, RA. Attention deficit hyperactivity disorder: A handbook for diagnosis and treatment. New York: Guilford; 1990.

Benedetto-Nasho R, Tannock R. Math computation, error patterns and stimulant effects in children with Attention Deficit Hyperactivity Disorder. J Attention Disorders. 1999; 3:121–134.

Berg EA. A simple objective treatment for measuring flexibility in thinking. J Gen Psychol. 1948; 39:15–22. [PubMed: 18889466]

Bowman RS, Stein LI, Newton JR. Measurement and interpretation of drinking behavior. Q J Stud Alcohol. 1975; 36:1154–1172.

Burden MJ, Jacobson SW, Jacobson JL. The relation of prenatal alcohol exposure to cognitive processing speed and efficiency in childhood. Alcohol Clin Exp Res. 2005b; 29:1473–1483. [PubMed: 16131856]

Burden MJ, Jacobson SW, Sokol RJ, Jacobson JL. Effects of prenatal alcohol exposure on attention and working memory at 7.5 years of age. Alcohol Clin Exp Res. 2005a; 29:443–452. [PubMed: 15770121]

Burden MJ, Jacobson JL, Westerlund A, Lundahl LH, Morrison MA, Dodge NC, Klorman R, Nelson CA, Avison MJ, Jacobson SW. An event-related potential study of response inhibition in ADHD with and without prenatal alcohol exposure. Alcohol Clin Exp Res. 2010; 34:617–627. [PubMed: 20102568]

Cantlon JF, Brannon EM, Carter EJ, Pelphrey KA. Functional imaging of numerical processing in adults and 4-yr-old children. PLOS Biology. 2006; 4:e125. [PubMed: 16594732]

Carlson CL, Pelham WE, Swanson JM, Wagner JL. A divided attention analysis of the effects of methylphenidate on the arithmetic performance of children with attention deficit hyperactivity disorder. J Child Psychol Psychiatr. 1991; 32:463–471.

Chochon F, Cohen L, van de Moortele PF, Dehaene S. Differential contributions of the left and right inferior parietal lobules to number processing. J Cog Neurosci. 1999; 11:617–630.

Coles CD, Brown RT, Smith IE, Platzman KA, Erickson S, Falek A. Effects of prenatal alcohol exposure at school age. I. Physical and cognitive development. Neurotoxicol Teratol. 1991; 13:357–367. [PubMed: 1921915]

Coles CD, Platzman KA, Lynch ME, Friedes D. Auditory and visual sustained attention in adolescents prenatally exposed to alcohol. Alcohol Clin Exp Res. 2002; 26:263–271. [PubMed: 11964567]

Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A, Smith IE. A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. Alcohol Clin Exp Res. 1997; 21:150–161. [PubMed: 9046388]

Crocker N, Vaurio L, Riley EP, Mattson SN. Comparison of adaptive behavior in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. Alcohol Clin Exp Res. 2009; 33:2015–2023. [PubMed: 19719794]

Davis N, Cannistraci CJ, Rogers BP, Gatenby JC, Fuchs LS, Anderson AW, Gore JC. The neural correlates of calculation ability in children: an fMRI study. Magnetic Resonance Imaging. 2009a; 27:1187–1197. [PubMed: 19570639]

Davis N, Cannistraci CJ, Rogers BP, Gatenby JC, Fuchs LS, Anderson AW, Gore JC. Aberrant functional activation in school age children at-risk for mathematical disability: A functional imaging study of simple arithmetic skill. Neuropsychol. 2009b; 47:2470–2479.

Dehaene, S. The number sense. Oxford: Oxford University Press; 1997.

Dehaene S, Cohen L. Cerebral pathways for calculation: Double dissociation between rote verbal and quantitative knowledge of arithmetic. Cortex. 1997; 33:219–250. [PubMed: 9220256]

Dehaene S, Molko N, Cohen L, Wilson AJ. Arithmetic and the brain. Current Opinion in Neurobiology. 2004; 14:218–224. [PubMed: 15082328]

Dehaene S, Piazza M, Pinel P, Cohen L. Three parietal circuits for number processing. Cog Neuropsychol. 2003; 20:487–506.

Delis, DC.; Kaplan, E.; Kramer, JH. Delis-Kaplan Executive Function System. San Antonio, TX: Psychological Corporation; 2001.

Dodge NC, Jacobson SW, Molteno CM, Pienaar M, Aitken L, Burden MJ, Hoyme HE, Robinson LK, Khaole N, Spelke E, Jacobson JL. Precursors of arithmetic deficits in fetal alcohol exposed children in Cape Town, South Africa. Alcohol Clin Exp Res. 2007; 31:183A.

DSM-IV. Diagnostic and statistical manual of mental disorders. 4th ed.. Washington, DC: American Psychiatric Association; 1994.

Eger E, Sterzer P, Russ MO, Giraud AL, Kleinschmidt A. A supramodal number representation in human intraparietal cortex. Neuron. 2003; 37:719–725. [PubMed: 12597867]

Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SM. Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. Pediatr. 2007; 119:e733–e741.

Geary DC. Mathematical disabilities: Cognitive, neuropsychological, and genetic components. Psychol Bull. 1994; 114:345–362. [PubMed: 8416036]

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]

Greenland, S.; Rothman, KJ. Introduction to stratified analysis, in Modern Epidemiology. Rothman, KJ.; Greenland, S., editors. Philadelphia: Lippincott, Williams, & Wilkins; 1998.

Gruber O, Indefrey P, Steinmetz H, Kleinschmidt A. Dissociating neural correlates of cognitive components in mental calculation. Cerebral Cortex. 2001; 11:350–359. [PubMed: 11278198]

Halperin JM, Schulz KP. Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). Psychol Bull. 2006; 132:560–581. [PubMed: 16822167]

Hollingshead, AB. Four Factor Index of Social Status. New Haven, CT: Yale University; 1975. Unpublished manuscript.

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]

Ischebeck A, Zamarian L, Siedentopf C, Koppelstatter F, Benke T, Felber S, Delazer M. How specifically do we learn? Imaging the learning of multiplication and subtraction. NeuroImage. 2006; 30:1365–1375. [PubMed: 16413795]

Jacobson JL, Jacobson SW. Methodological considerations in behavioral toxicology of infants and children. Dev Psychol. 1996; 32:390–403.

Jacobson JL, Jacobson SW, Sokol RJ, Martier SS, Ager JW, Kaplan-Estrin MG. Teratogenic effects of alcohol on infant development. Alcohol Clin Exp Res. 1993; 17:174–183. [PubMed: 8452200]

Jacobson SW, Chiodo LM, Jacobson JL, Sokol RJ. Validity of maternal report of alcohol, cocaine, and smoking during pregnancy in relation to infant neurobehavioral outcome. Pediatr. 2002a; 109:815–825.

Jacobson SW, Hay A, Molteno C, Marais AS, Carter RC, September M, Chiodo LM, Wynn K, Jones KL, Khaole N, Viljoen D, Jacobson JL. FAS and neurobehavioral deficits in alcohol-exposed South African infants. Alcohol Clin Exp Res. 2002b; 26:175A.

Jacobson SW, Jacobson JL, Sokol RJ. Effects of fetal alcohol exposure on infant reaction time. Alcohol Clin Exp Res. 1994; 18:1125–1132. [PubMed: 7847594]

Jacobson SW, Jacobson JL, Sokol RJ, Chiodo LM, Corobana R. Maternal age alcohol abuse history, and quality of parenting as moderators of the effects of prenatal alcohol exposure on 7.5-year intellectual function. Alcohol Clin Exp Res. 2004; 28:1732–1745. [PubMed: 15547461]

Jacobson SW, Jacobson JL, Sokol RJ, Martier SS, Ager JW. Prenatal alcohol exposure and infant information processing ability. Child Dev. 1993; 64:1706–1721. [PubMed: 8112114]

Jensen PS, Keffle L, Roper MT, Sloan MT, Dulcan MK, Hoven C, Bird HR, Bauermeister JJ, Payne JD. Are stimulants over prescribed? Treatment of ADHD in four U.S. communities. J Am Acad Child Adolescent Psychiatr. 1999; 38:797–804.

Kaufman L, Koppelstaetter F, Siedentopf C, Haala I, Haberlandt E, Zimmerhackl L, Felber S, Ischebeck A. Neural correlates of the number-size interference task in children. Neuroreport. 2006; 17:587–591. [PubMed: 16603917]

Kerns KA, Don A, Mateer CA, Streissguth AP. Cognitive deficits in nonretarded adults with Fetal Alcohol Syndrome. J Learn Disabilities. 1997; 30:685–693.

Kodituwakku PW, Handmaker NS, Cutler SK, Weathersby EK, Handmaker SD. Specific impairments in self-regulation in children exposed to alcohol prenatally. Alcohol Clin Exp Res. 1995; 19:1558–1564. [PubMed: 8749827]

Kopera-Frye K, Dehaene S, Streissguth AP. Impairments of number processing induced by prenatal alcohol exposure. Neuropsychologia. 1996; 34:1187–1196. [PubMed: 8951830]

Kucian K, Loenneker T, Dietrich T, Dosch M, Martin E, von Aster M. Impaired neural networks for approximate calculation in dyscalculic children: A functional MRI study. Behav Brain Functions. 2006; 2:31–48.

Lindsay RL, Tomazic T, Levine MD, Accardo PJ. Impact of attentional dysfunction in dyscalculia. Dev Med Child Neurol. 1999; 41:639–642. [PubMed: 10503923]

Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol. 1993; 138:923–936. [PubMed: 8256780]

Mattson SN, Riley EP, Delis DC, Stern C, Jones KL. Verbal learning and memory in children with fetal alcohol syndrome. Alcohol Clin Exp Res. 1996; 20:810–816. [PubMed: 8865953]

Meintjes EM, Jacobson SW, Molteno CD, Gatenby JC, Warton C, Cannistraci CJ, Gore JC, Jacobson JL. An fMRI study of number processing in children. Magnetic Resonance Imaging. 2010; 28:351–362. [PubMed: 20116955]

Meintjes EM, Jacobson JL, Molteno CD, Gatenby JC, Warton C, Cannistraci CJ, Hoyme EH, Robinson LK, Khaole N, Gore JC, Jacobson SW. An fMRI study of number processing in children with fetal alcohol syndrome. Alcohol: Clin Exp Res. (In press).

Menon V, Rivera SM, White CD, Glover GH, Reiss AL. Dissociating prefrontal and parietal cortex activation during arithmetic processing. Neuroimage. 2000; 12:357–365. [PubMed: 10988030]

Mick E, Biederman J, Faraone SV, Sayer J, Kleinman S. Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use drug use during pregnancy. J Am Acad Child Adolescent Psychiatr. 2002; 41:378–385.

Naccache L, Dehaene S. The priming method: imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. Cereb Cortex. 2001; 11:966–974. [PubMed: 11549619]

Nanson JL, Hiscock M. Attention deficits in children exposed to alcohol prenatally. Alcohol Clin Exp Res. 1990; 14:656–661. [PubMed: 2264593]

O'Malley KD, Koplin B, Dohner VA. Psychostimulant clinical response in fetal alcohol syndrome. Canadian J Psychiatr. 2000; 45:90–91.

Pelham WE, Gnagy EM, Greenslade KE, Milich R. Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders. J Am Acad Child Adolescent Psychiatr. 1992; 31:210–218.

Pesenti M, Thioux M, Seron X, De Volder A. Neuroanatomical substrates of Arabic number processing, numerical comparison, and simple addition: A PET study. J Cog Neurosci. 2000; 12:461–479.

Pinel P, Piazza M, Le Bihan D, Dehaene S. Distributed and overlapping cerebral representations of number, size, and luminance during comparative judgments. NeuroImage. 2004; 41:983–993.

Price GR, Holloway I, Rasanen P, Verterinen M, Ansari D. Impaired parietal magnitude in processing in developmental dyscalculia. Curr Biol. 2007; 17:R1042–R1043. [PubMed: 18088583]

Rasmussen C, Bisanz J. Exploring mathematics difficulties in children with fetal alcohol spectrum disorders. Child Dev Perspect. 2009; 3:125–130.

Rubinsten O, Bedard AC, Tannock R. Methylphenidate has differential effects on numerical abilities in ADHD children with and without co-morbid mathematical difficulties. Open Psychol J. 2008; 1:11–17.

Sattler, JM. Assessment of Children. 3rd ed.. San Diego: Jerome M. Sattler, San Diego; 1992.

Shekim WO, Kashani J, Beck N, Cantwell DP, Martin J, Rosenberg J, Costello A. The prevalence of attention deficit disorder in a rural Midwestern community sample of nine-year-old children. J Am Acad Child Adolescent Psychiatr. 1985; 24:765–770.

Simon O, Mangin JF, Cohen L, Le Bihan D, Dehaene S. Topographical layout of hand eye calculation, and language-related areas in the human parietal lobe. Neuron. 2002; 33:475–487. [PubMed: 11832233]

Sobel, ME. Asymptotic confidence intervals for indirect effects in structural equation models. In: Leinhardt, S., editor. Sociological Methodology. Washington, DC: American Sociological Association; 1982. p. 290-312.

Sokol, RJ.; Martier, S.; Ernhart, C. Identification of alcohol abuse in the prenatal clinic, in. In: Chang, NC.; Chao, HM., editors. Early Identification of Alcohol Abuse. Rockville, MD: Alcohol, Drug Abuse, and Mental Health Administration Research Monograph No. 17; 1985. p. 85-128.

Sowell ER, Mattson SN, Kan E, Thompson PM, Riley ER, Toga AW. Abnormal cortical thickness and brain-behavior correlation patterns in individuals with heavy prenatal alcohol exposure. Cerebral Cortex. 2008; 18:126–144. [PubMed: 17470446]

Sowell ER, Thompson PM, Mattson SN, Tessner KD, Jernigan TL, Riley EP, Toga AW. Voxel-based morphometric analyses of the brain in children and adolescents prenatally exposed to alcohol. NeuroReport. 2001; 12:515–523. [PubMed: 11234756]

Sowell ER, Thompson PM, Mattson SN, Tessner KD, Jernigan TL, Riley EP, Toga AW. Regional brain shape abnormalities persist into adolescence after heavy prenatal alcohol exposure. Cerebral Cortex. 2002; 12:856–865. [PubMed: 12122034]

Spreen, O.; Strauss, E. A compendium of neuropsychological tests. New York: Oxford University Press; 1991.

Stanescu-Cossin R, Pinel P, van de Moortele P-F, Le Bihan D, Cohen L, Dehaene S. Understanding dissociations in dyscalculia: A brain imaging study of the impact of number size on the cerebral networks for exact and approximate calculation. Brain. 2000; 123:2240–2255. [PubMed: 11050024]

Steinhausen HC, Willms J, Spohr HL. Long-term psychopathological and cognitive outcome of children with fetal alcohol syndrome. J Am Acad Child Adolescent Psychiatr. 1993; 32:990–994.

Sternberg S. High speed scanning in human memory. Science. 1966; 153:652–654. [PubMed: 5939936]

Streissguth AP, Aase JM, Clarren SK, Randels SP, LaDue RA, Smith DF. Fetal alcohol syndrome in adolescents and adults. JAMA. 1991; 265:1961–1967. [PubMed: 2008025]

Streissguth AP, Barr HM, Carmichael-Olson H, Sampson PD, Bookstein FL, Burgess DM. 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]

Streissguth AP, Barr HM, Sampson PD. Moderate prenatal alcohol exposure: Effects on child IQ and learning problems at age 7 ½ years. Alcohol Clin Exp Res. 1990; 14:662–669. [PubMed: 2264594]

Temple E, Posner MI. Brain mechanisms of quantity are similar in 5-year-old children and adults. Proc Natl Acad Sci USA. 1998; 95:7836–7841. [PubMed: 9636237]

Vaurio L, Riley EP, Mattson SM. Differences in executive functioning in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. J Int Neuropsychol Soc. 2008; 14:119–129. [PubMed: 18078538]

Wechsler, D. Wechsler Individual Achievement Test. San Antonio, TX: Psychological Corporation; 1992.

Wechsler, D. Wechsler Intelligence Test for Children. 3rd edition. San Antonio, TX: Psychological Corporation; 1992.

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; 23:497–507. [PubMed: 15084908]

Winer, BJ. Statistical principles in experimental design. 2nd ed. New York: McGraw-Hill; 1971.

Wynn K, Bloom P, Chiang WC. Enumeration of collective entities by 5-month-old infant. Cognition. 2002; 83:B55–B62. [PubMed: 11934407]

Zago L, Pesenti M, Mellet E, Crivello F, Mazoyer B, Tzourio-Mazoyer N. Neural correlates of simple and complex mental calculation. Neuroimage. 2001; 13:314–327. [PubMed: 11162272]

Zago L, Petit L, Turbelin M, Andersson F, Vigneau M, Tzourio-Mazoyer N. How verbal and spatial manipulation networks contribute to calculation: An fMRI study. Neuropsychologia. 2008; 46:2403–2414. [PubMed: 18406434]

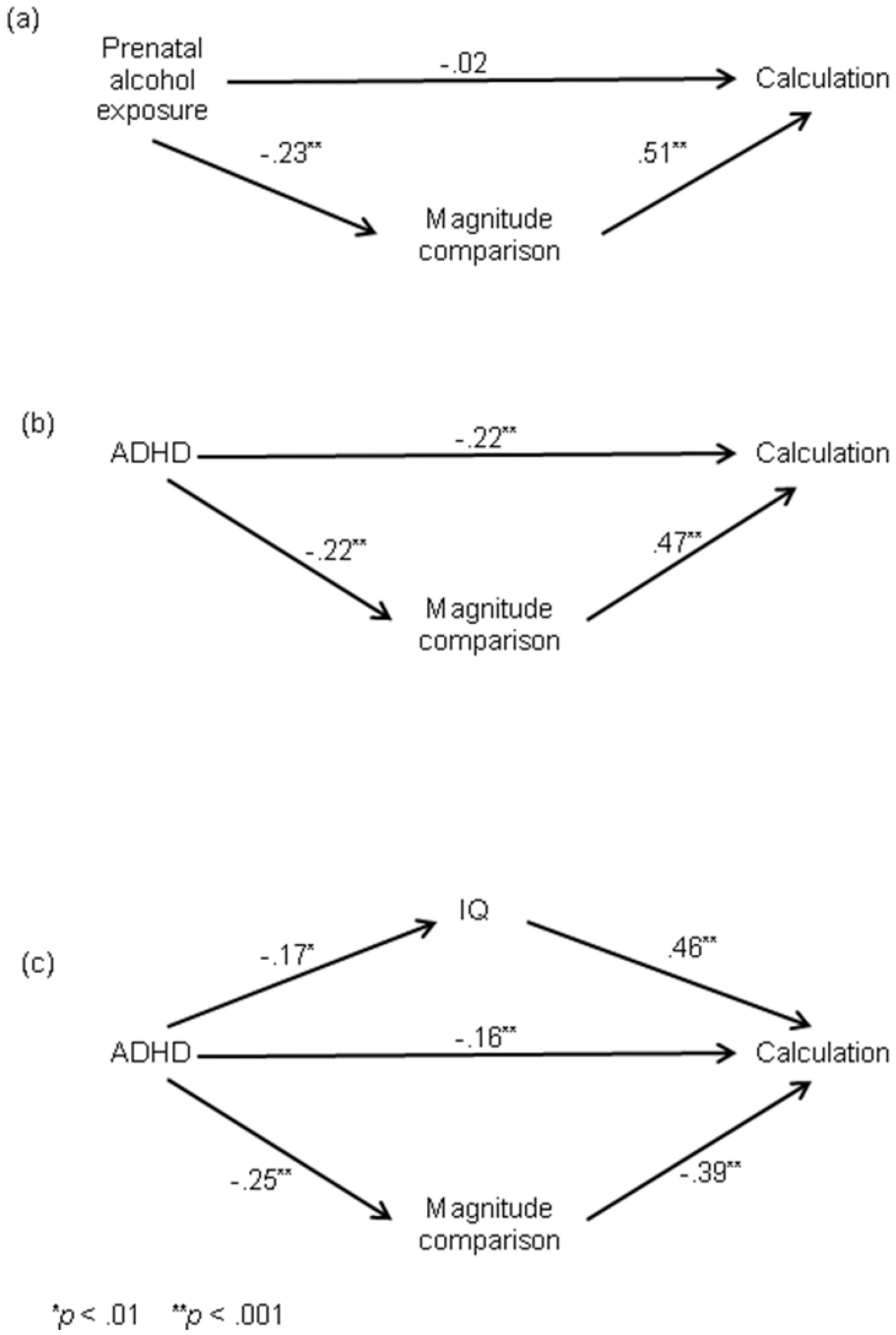

Figure 1.

Path models examining (a) the degree to which the relation of prenatal alcohol exposure to the calculation composite score is mediated by magnitude comparison; (b) the degree to which the relation of ADHD to the calculation composite score is mediated by magnitude comparison; and (c) the effect of adding IQ to the model for ADHD. The model examining the effect of prenatal alcohol exposure is adjusted statistically for gender; none of the control variables met criteria for inclusion in the models examining ADHD.

Table 1

Sample characteristics ($N = 262$)

	M or %	SD
Age at assessment (years)	14.4	0.6
Gender (% male)	57.6	
Socioeconomic status[a]	29.7	10.1
Primary caregiver's education (years)	12.5	1.8
Primary caregiver's verbal competence[b]	74.4	13.3
Maternal age at delivery	27.0	6.0
Alcohol use during pregnancy (oz AA/day)[c]	0.3	0.7
Standard drinks of alcohol/occasion during pregnancy[c]	3.5	3.4
Frequency of alcohol consumption during pregnancy (days/month)[c]	4.3	5.0
Smoking during pregnancy (cigarettes/day)[d]	15.4	12.1
Cocaine use during pregnancy (% ≥ once/week)	21.0	
Marijuana use during pregnancy (days/month)[e]	3.2	3.5
ADHD (% meeting diagnostic criteria)	32.8	
Predominantly inattentive type (%)	9.9	
Predominantly hyperactive-impulsive type (%)	2.7	
Combined type (%)	20.2	
Adolescent alcohol use (oz AA/month)[f]	2.0	2.4
Adolescent smoking (cigarettes/month)[g]	25.8	27.8
Adolescent marijuana use (days/month)[h]	4.7	4.6
Full Scale IQ (WISC-III)	79.2	12.7
WIAT Mathematics Reasoning standard score[i]	83.7	11.8

[a] Hollingshead (1975) scale

[b] Peabody Picture Vocabulary Test-Revised

[c] 82.4% of the mothers drank during pregnancy. Means are shown for those who drank.

[d] 62.2% of the mothers smoked during pregnancy. Means are shown for those who smoked.

[e] 30.2% of the mothers used marijuana during pregnancy. Means are shown for those who used marijuana.

[f] Adolescent alcohol use data are available for 208 participants. Means are shown for the 27 who used alcohol.

[g] Adolescent smoking data are available for 213 participants. Means are shown for the 8 who smoked.

[h] Adolescent marijuana use data are available for 214 participants. Means are shown for the 13 who used marijuana.

[i] The WIAT was not administered for seven cases.

Table 2

Relation of prenatal alcohol exposure (oz AA/day) to ADHD

	Prenatal alcohol exposure[a]				
	Abstainer (0)	**Light (.01–.49)**	**Moderate (.5–.99)**	**Heavy (1.0+)**	**Total**
ADHD					
No	41	114	11	10	176
	(89.1%)	(63.3%)	(61.1%)	(55.6%)	(67.2%)
Yes	5	66	7	8	86
	(10.9%)	(36.7%)	(38.9%)	(44.4%)	(32.8%)
Total	46	180	18	18	262
	(100.0%)	(100.0%)	(100.0%)	(100.0%)	(100.0%)

χ^2 (3) = 12.66, $p < .005$.

[a] oz AA/day.

Table 3

Factor analysis of the seven number processing subtests ($N = 262$)

	I Calculation	II Magnitude Comparison
Exact addition	**.79**	.19
Exact subtraction	**.85**	.23
Exact multiplication	**.86**	.08
Approximate addition	**.78**	.32
Approximate subtraction	**.81**	.27
Number comparison	.09	**.88**
Proximity judgment	.37	**.68**

Values are factor loadings. Bold face type indicates the factor on which the item loaded most strongly.

Alcohol Clin Exp Res. Author manuscript; available in PMC 2012 August 13.

Table 4

Multiple regression analyses of the number processing subtests and composite scores on prenatal alcohol exposure (log AA/day) and ADHD ($N = 262$)

	Prenatal Alcohol			ADHD		
	r	β_1	β_2	*r*	β_1	β_2
Exact addition[a]	−.12†	−.07	−.05	−.27***	−.27***	−.19***
Exact subtraction[b]	−.10	−.07	−.02	−.31***	−.31***	−.23***
Exact multiplication[c]	−.13*	−.11†	−.07	−.29***	−.29***	−.21***
Approximate addition[d]	−.12†	−.09	−.05	−.24***	−.24***	−.17**
Approximate subtraction	−.17**	−.17**	−.13*	−.30***	−.30***	−.22***
Number comparison	−.27***	−.27***	−.25***	−.14*	−.14*	−.12†
Proximity judgment[e]	−.22***	−.24***	−.22***	−.23***	−.20**	−.17**
Calculation subtests composite[f]	−.15*	−.14*	−.09†	−.34***	−.34***	−.24***
Magnitude comparison subtests composite[g]	−.23***	−.25***	−.23***	−.25***	−.22**	−.19***

$^{\dagger}p < .10$

$^{*}p < .05$

$^{**}p < .01$

$^{***}p < .001$

β_1: Controlling for confounders

β_2: Controlling for confounders and IQ

[a] Controlling for gender, mother's age at delivery, and primary caregiver's years of education in the prenatal alcohol analyses.

[b] Controlling for primary caregiver's years of education and Peabody vocabulary score, gender, and maternal smoking during pregnancy in the prenatal alcohol analyses.

[c] Controlling for gender in the prenatal alcohol analyses.

[d] Controlling for maternal smoking during pregnancy in the prenatal alcohol analyses.

[e] Controlling for maternal smoking and heavy cocaine use during pregnancy in the prenatal alcohol analyses. Controlling for gender in the ADHD analyses.

[f] Controlling for gender in the prenatal alcohol analyses.

[g] Controlling for maternal smoking and heavy cocaine use during pregnancy in the prenatal alcohol analyses. Controlling for gender in the ADHD analyses.

Table 5

Multiple regression analyses of the number processing composite scores evaluating the effects of prenatal alcohol exposure (log AA/day) and ADHD simultaneously ($N = 262$)

	Prenatal Alcohol			ADHD		
	r	**β_1**	**β_2**	***r***	**β_1**	**β_2**
Calculation subtests composite[a]	−.15*	−.11*	−.11†	−.34***	−.32***	−.31***
Magnitude comparison subtests composite[b]	−.23***	−.20***	−.21***	−.25***	−.22***	−.20**

$^{\dagger}p < .10$

$^{*}p < .05$

$^{**}p < .01$

$^{***}p < .001$

β_1: Effect when both prenatal alcohol and ADHD were entered simultaneously in the analysis.

β_2: Effect when prenatal alcohol, ADHD, and the relevant potential confounders were all included in the analysis.

[a] Controlling for gender.

[b] Controlling for maternal smoking, heavy cocaine use, and gender.