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Neurobehavioral Deficits Consistent Across Age and Sex in Youth with Prenatal Alcohol Exposure

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Abstract

Background—Neurobehavioral consequences of heavy prenatal alcohol exposure are well documented, however the role of age or sex in these effects has not been studied. The current study examined the effects of prenatal alcohol exposure, sex, and age on neurobehavioral functioning in children.

Methods—Subjects were 407 youth with prenatal alcohol exposure ($n=192$) and controls ($n=215$). Two age groups [child (5–7y) or adolescent (10–16y)] and both sexes were included. All subjects completed standardized neuropsychological testing and caregivers completed parent-report measures of psychopathology and adaptive behavior. Neuropsychological functioning, psychopathology, and adaptive behavior were analyzed with separate 2 (exposure history) $\times$ 2 (sex) $\times$ 2 (age) MANOVAs. Significant effects were followed by univariate analyses.

Results—No three-way or two-way interactions were significant. The main effect of group was significant in all three MANOVAs, with the control group performing better than the alcohol-exposed group on all measures. The main effect of age was significant for neuropsychological performance and adaptive functioning across exposure groups with younger children performing

better than older children on three measures (language, communication, socialization). Older children performed better than younger children on a different language measure. The main effect of sex was significant for neuropsychological performance and psychopathology; across exposure groups, males had stronger language and visual-spatial scores and fewer somatic complaints than females.

Conclusion—Prenatal alcohol exposure resulted in impaired neuropsychological and behavioral functioning. Although adolescents with prenatal alcohol exposure may perform more poorly than younger exposed children, the same was true for non-exposed children. Thus, these cross-sectional data indicate that the developmental trajectory for neuropsychological and behavioral performance is not altered by prenatal alcohol exposure, but rather, deficits are consistent across the two age groups tested. Similarly, observed sex differences on specific measures were consistent across the groups and do not support sexually dimorphic effects in these domains.

Keywords

fetal alcohol spectrum disorders; behavior; neuropsychological function; sex; age

Introduction

Children and adolescents with histories of prenatal alcohol exposure are at risk for fetal alcohol spectrum disorders (FASD), which are characterized by neuropsychological and behavioral impairments (Mattson et al., 2011, Bertrand et al., 2005, Streissguth and O'Malley, 2000). Some of the most prominent deficits associated with prenatal alcohol exposure include those in executive functioning, learning, and attention (Mattson et al., 2011). Impairments in language, motor functioning, and visual-spatial ability, as well as lower general intellectual ability, are also observed in individuals with FASD (Mattson and Riley, 1998, Mattson et al., 2011). Behaviorally, diminished social competency, limited daily living skills, and increased externalizing problems are often observed compared to typically developing controls.

While the behavioral and neurocognitive effects of prenatal alcohol exposure have been widely studied (for review, see Mattson et al., 2011), how these effects may vary with sex or age has received less attention. Sex differences are well-documented in other developmental disorders, such as attention-deficit/hyperactivity disorder (ADHD), conduct disorder, and autism (Boyle et al., 2011, Maughan et al., 2004). For example, ADHD is more prevalent in boys than girls (Boyle et al., 2011, DuPaul et al., 1998), and results from a large-scale meta-analysis suggest that ADHD symptomology varies between sexes (Gaub and Carlson, 1997). Given the high rates of ADHD in the FASD population (Fryer et al., 2007), sex differences in the cognitive and behavioral effects are possible and documentation of these differences could improve identification of affected individuals.

Sex differences after prenatal exposure to alcohol have been observed in the rate and type of secondary disabilities, such as school disruptions, delinquency, inappropriate sexual behavior, and substance abuse problems (Streissguth, 2012). It is possible that environmental factors outside of prenatal alcohol exposure may contribute to these differences and in general, most studies investigating neuropsychological performance and behavior in humans

with prenatal alcohol exposure have not explored sex effects, perhaps due to limitations of sample size. While animal studies have addressed sex effects after prenatal exposure to alcohol more extensively than human studies have, many of these studies lack sufficient power to detect interactive effects, decreasing reliability of the results (see Otero and Kelly, 2012). One replicated effect is that prenatal alcohol exposure lowers testosterone levels in male rodent fetuses, reducing the differentiation of the male brain, ultimately causing the brains of males with prenatal alcohol exposure to be feminized (see Otero and Kelly, 2012). Such an effect may result in the absence of typical sexual dimorphism in behavior or cognitive ability among those with prenatal exposure to alcohol, but insufficient research with humans limits this conclusion.

In terms of age, most studies investigating the neurobehavioral effects of prenatal alcohol exposure control for expected differences across development by analyzing age-corrected scores or including age as a covariate. While investigating these impairments by controlling for age differences in this manner is important, directly assessing the relationship of age with these neurobehavioral effects may provide greater diagnostic clarity by specifying whether deficits differ by age. Some neurobehavioral studies have explicitly addressed the role of age (e.g., Crocker et al., 2011), however such studies are limited in number and the precise relationship between age and neurobehavioral impairments is not fully understood. Relative to other functional domains, the role of age in adaptive deficits has been relatively well studied. Three studies indicated that adaptive functioning worsens with age in alcohol-exposed individuals, relative to control subjects (Crocker et al., 2009, Thomas et al., 1998, Whaley et al., 2001). Although the interaction of age and prenatal alcohol exposure on neuropsychological functioning is not well studied, one study examined the role of age on executive functioning in a small sample of children prenatally exposed to alcohol, and reported that deficits in verbal inhibition and switching, verbal fluency, and verbal abstract reasoning were greater in older children than younger children (Rasmussen and Bisanz, 2009). However, there was no control group against which to compare the developmental trajectory of the exposed group. Thus, while limited, previous findings suggest that cognitive ability does not keep pace as cognitive demands increase with age in alcohol-exposed individuals. Improved understanding of how neurobehavioral deficits relate to prenatal alcohol exposure change with age may improve identification of FASD by providing a rationale for examining age-specific symptoms (Mattson and Riley, 2011).

The current study examined the effects of age and sex on neuropsychological and behavioral function in children with histories of prenatal alcohol exposure and non-exposed control children. We hypothesized that children with prenatal alcohol exposure would perform worse on all neuropsychological tasks, display higher rates of psychopathology, and lower adaptive functioning competency compared to controls. Based on the findings highlighted above, we expected these differences would be more robust in older children than younger children, with no age effects anticipated in the control group, as our tests were normed by age. In the control group and across age groups, we expected that boys would perform better on nonverbal reasoning and visual-spatial tasks, while girls would perform better on language and memory tasks (Halpern and LaMay, 2000). We anticipated that these sex differences in neuropsychological functioning would be less robust in the alcohol-exposed children, across age groups. Even so, we expected boys with prenatal alcohol exposure to

display greater externalizing psychopathology and attention problems, and poorer socialization scores compared to alcohol-exposed girls (Zahn-Waxler et al., 2008).

Materials and Methods

General Method

The current study is part of a larger, ongoing study within the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). Data collection began for the current phase in November 2013 (Phase 3, CIFASD-III) at four sites across the United States: Atlanta, GA, Los Angeles, CA, Minneapolis, MN, and San Diego, CA (for details, see Mattson et al., 2010).

Trained examiners, blind to subject group, administered a three-hour standardized neuropsychological assessment battery in a room with minimal distractions. This assessment battery (described below) included standardized measures of a variety of cognitive domains including executive functioning and attention, language ability, learning and memory, nonverbal reasoning, and visual-spatial ability. Additionally, each child's caregiver completed several parent-reported assessments, measuring child psychopathology and adaptive functioning as well as providing demographic, medical, and academic information for the child. Subject incentive payments were made to both child and caregiver. The Institutional Review Boards at San Diego State University and all participating data collection sites approved the study procedures.

Subjects

Subjects ($N=407$) included males and females with histories of prenatal alcohol exposure (AE; $n=192$) and typically developing controls (CON; $n=215$). As one of the aims of CIFASD-III is to examine the effects of age, two distinct age groups were assessed; subjects were either 5–7 years of age (child) or 10–16 years of age (adolescent). All group demographic information is displayed in Table 1.

Subjects were recruited via schools, clinics, professional referrals, community outreach, advertisements, word of mouth, or other public forums, such as the Internet. Subjects were excluded from participation if English was not their primary language, if they were adopted from abroad either after the age of five or within two years of the assessment, had ever suffered a significant head injury and/or a loss of consciousness (>30 minutes), or had a known severe mental, physical or psychiatric disability that hindered study participation (e.g., active psychosis, active mania, uncontrolled movement disorders, blindness). All subjects in the AE group had histories of heavy prenatal alcohol exposure, which was defined as maternal consumption of more than four alcoholic drinks per occasion at least once a week, or more than 13 drinks, on average, per week throughout gestation. Exposure histories for all subjects were retrospectively confirmed through a variety of methods including birth records, medical history, records from social services, and maternal reports, when available. In many cases, precise details on prenatal exposure were unavailable. In such cases, subjects were included if the biological mother was considered to be “alcoholic,” alcohol abusing, or alcohol dependent during pregnancy. Subjects were also included in

CIFASD studies if exposure was suspected and the child met criteria for FAS, as described below, although this did not occur in this group of subjects. Subjects in the CON groups were recruited from the communities of all four sites as typically developing children, and were included only if they were exposed to less than one drink per week, on average, and never more than two drinks per occasion during pregnancy, by maternal report.

A dysmorphologist examined all subjects for diagnostic features of FAS, as defined by the CIFASD dysmorphology core (KL Jones, Principal Investigator; Jones et al., 2006). Diagnostic criteria included two or more of the following facial features: thin vermilion border, smooth philtrum, and short palpebral fissure length, and either microcephaly (occipital-frontal circumference $\geq 10\%$) or growth deficiency (height or weight $\geq 10\%$) (Jones et al., 2006, Mattson et al., 2010).

Measures

NEPSY-II—The NEPSY-II (Korkman et al., 2007) is a comprehensive neuropsychological assessment for children and adolescents. The NEPSY-II has demonstrated utility in the pediatric FASD population (Paolozza et al., 2014) and all scores are normed by age. The assessment has established high internal consistency, test-retest reliability and inter-rater reliability, and adequate validity (Korkman et al., 2007). Select subtests that were included in the present study are described in detail in Table 2.

Differential Ability Scales—Second Edition (DAS-II)—The DAS-II (Elliott, 2007) is an assessment battery of cognitive measures that provides a general conceptual ability (GCA) score. Like an IQ score, the GCA approximates the general ability of each subject to perform complex mental processing, and is used to approximate overall cognitive ability in this study. All subtests in the DAS-II are normed by age and have been well validated in typically developing and clinical child populations (Elliott, 2007). The correlation of the DAS-II GCA and the full scale IQ score from the Wechsler Intelligence Scale for Children (WISC-IV) is .84 (Dumont et al., 2009). Additionally, the DAS-II has demonstrated convergent and discriminant validity, as well as reliability in these populations (Elliott, 2007). Select DAS-II subtests that were included in the present study are described in Table 2.

Child Behavior Checklist (CBCL)—The CBCL (Achenbach and Rescorla, 2001) is a 113-item assessment completed by the subject's caregiver that provides information about psychopathology, including behavioral and emotional functioning. The CBCL has been frequently used in studies addressing behavioral problems in youth with prenatal alcohol exposure (Mattson and Riley, 2000, Sood et al., 2001, Staroselsky et al., 2009, Steinhausen and Spohr, 1998). All scores are standardized by age and sex. The CBCL (school-age version) has demonstrated content, construct, and criterion-related validity, as well as very high inter-rater and test-retest reliability (Achenbach and Rescorla, 2001). CBCL syndrome scales included in the study are described in Table 3.

Vineland Adaptive Behavior Scales-Second Edition (VABS-II)—The VABS-II interview (Sparrow et al., 2005) is a caregiver-reported assessment that addresses a child's

adaptive functioning and has been used in previous studies of adaptive functioning in alcohol-exposed children (Crocker et al., 2009, Kelly et al., 2000). All scores are standardized by age. This assessment has proven reliability and validity in both typically developing and clinical child populations (Sparrow et al., 2005). VABS-II scales included in the present study are described in Table 3.

Statistical Analyses

The SPSS statistical software package version 22.0 (IBM Corp., Armonk, NY) was used for all analyses. The AE and CON groups were compared on demographic variables using chi-square (ethnicity, handedness, race and sex) and standard analysis of variance (ANOVA) techniques (age, GCA, and socio-economic status [SES], as measured by the Hollingshead 4-factor index). Three separate MANOVAs with a 2 (Exposure History: AE, CON) $\times$ 2 (Age Group: child, adolescent) $\times$ 2 (Sex: male, female) design were used to measure: (1) neuropsychological performance (NEPSY-II and DAS-II), (2) psychopathology (CBCL), and (3) adaptive functioning (VABS-II). Behavioral data were analyzed by two separate MANOVAs because the assessment tools measure two different aspects of functioning, and the CBCL, which measures psychopathology, is normed by age and sex, while the VABS-II, which measures adaptive functioning, is only normed by age. Both the NEPSY-II and the DAS-II are normed by age only, so the neuropsychological data was analyzed with one MANOVA. Wilks' criterion (Λ) was used as the omnibus test statistic. A Bonferroni correction was used to control for Type 1 error (.05/3), so results were considered to be significant at an alpha of $p < .017$ and marginally significant at an alpha of .017 $p < .023$ (.07/3). Significant interactions were followed up with univariate simple effects tests.

Assessment for Outliers and Covariates

All variables were assessed for outliers prior to analyses using a boxplot analysis, and scores more than three standard deviations above or below the mean were considered outliers and deleted from the neuropsychological analysis. Two subjects, both from the AE group, met this criterion and were removed from the neuropsychological analysis. Due to the predicted low variability for the behavioral measures in the CON group, subjects were only considered to be outliers for the behavioral analyses if they were three standard deviations above or below the group mean and if they were two standard deviations above or below the normative mean. Five subjects from the CON group met these criteria and were removed from the psychopathology analysis, and no subjects were removed as outliers from the adaptive functioning analysis. All scores from subjects in the AE group were within three standard deviations of the group means for the behavioral measures, so no data points from this group were considered to be outliers. Subjects missing data for one or more of the subtests included in a MANOVA were excluded from that particular analysis, but may have been included in the remaining analyses.

Demographic variables were included as covariates if they met all statistical assumptions necessary for appropriate use as a covariate.

Results

Demographics

The AE and CON groups did not differ significantly on age [$F(1, 406) = .45, p = .504$], ethnicity [$\chi^2 (df = 1) = 1.68, p = .195$], handedness [$\chi^2 (df = 3) = 2.78, p = .426$], race [$\chi^2 (df = 7) = 15.30, p = .032$], SES [$F(1, 306) = 2.10, p = .149$], sex [$\chi^2 (df = 1) = .002, p = .963$], or site [$\chi^2 (df = 3) = 1.97, p = .578$]. Groups differed significantly on GCA [$F(1, 403) = 110.12, p < .001$]. Children in the CON group had higher GCA scores than children with prenatal alcohol exposure. Group demographics are displayed in Table 1.

Furthermore, since data were collected from multiple sites, site differences for demographic variables were assessed. We found that race, handedness, ethnicity and age group differed significantly by site ($ps = .032$). To ensure that these site differences did not influence our results, we re-ran the analysis using a 2 (Exposure History: AE, CON) $\times$ 2 (Age Group: child, adolescent) $\times$ 2 (Sex: male, female) $\times$ 4 (Site: Atlanta, Los Angeles, Minneapolis, San Diego) design. The four-way interactions for the three MANOVAs were not significant (Neuropsychological Functioning: $p = .789$; CBCL: $p = .197$; VABS-II: $p = .497$), indicating that the effects of demographic variables did not affect the groups differently by site and was not included in subsequent analyses.

Neuropsychological Performance—Subject handedness was considered an appropriate covariate and was initially included as a covariate in the neuropsychological MANOVA. This variable was not significant in the MANOVA, and consequently removed from the analysis to preserve parsimony. This removal did not alter the results. Using an alpha level of .001 to evaluate homogeneity assumptions, Box's M test of homogeneity of covariance was not statistically significant ($p = .003$). Levene's test for equality of variances was also not significant for all measures ($ps = .001$), except Memory for Names Delayed (MND; $p < .001$).

Average neuropsychological performance scores are available in the supplemental table and statistical results are listed in Table 4. For neuropsychological performance, there were no significant interactions between group, sex, and age ($ps = .174$). However, there were significant main effects of exposure [$F(13, 356) = 12.67, p < .001$, partial $\chi^2 = .316$], age [$F(13, 356) = 4.26, p < .001$, partial $\chi^2 = .135$], and sex [$F(15, 356) = 3.81, p < .001$, partial $\chi^2 = .122$]. Follow-up analyses indicated that the AE group performed significantly worse than the CON group on all measures of neuropsychological functioning ($ps = .001$).

Additionally, the child group performed significantly better than the adolescent group on Verbal Similarities (VS; $p = .001$) subtests, but significantly worse on Word Generation Semantic (WGS; $p < .001$). There were no other significant effects of age on DAS-II or NEPSY-II measures ($ps = .130$). Regarding sex, males performed significantly better than females on Arrows (AW; $p < .001$), and Word Definitions (WD; $p = .010$). A summary of the results are displayed in Table 4 and illustrated in Figure 1.

Parent Ratings of Problem Behaviors—Using an alpha level of .001 to evaluate homogeneity assumptions, Box's M test of homogeneity of covariance and Levene's test for equality of variances were both significant ($ps < .001$), indicating that the data violated the

assumptions of homogeneity of variance, although MANOVA is robust to this violation. For the CBCL syndrome scales, there were no significant interactions between exposure history, sex, and age ($p = .114$), and no main effect of age ($p = .935$). There were significant main effects of exposure [$F(8, 345) = 51.82, p < .001$, partial $\chi^2 = .546$] and sex [$F(8, 345) = 2.47, p = .013$, partial $\chi^2 = .054$]. Follow-up analyses demonstrated that the AE group had significantly higher scores than the CON group on all CBCL syndrome scales ($p < .001$), demonstrating increased levels of psychopathology. Regarding sex, follow-up analyses indicated that males had marginally fewer somatic complaints than females ($p = .023$). A summary of the results are displayed in Table 4 and illustrated in Figure 2.

Parent Ratings of Adaptive Function—An alpha level of .001 to evaluate homogeneity assumptions was also used for the VABS-II domain. Box's M test of homogeneity of covariance was not statistically significant ($p = .002$). Levene's test for equality of variances was not significant for Daily Living Skills and Socialization ($p = .002$), but was significant for Communication ($p < .001$). There were no significant interactions between exposure history, sex, and age ($p = .026$) or a main effect of sex ($p = .347$). There were significant main effects of exposure [$F(3, 389) = 106.00, p < .001$, partial $\chi^2 = .450$] and age [$F(3, 389) = 15.47, p < .001$, partial $\chi^2 = .107$]. Follow-up analyses illustrated that the AE group scored significantly worse than the CON group on all domains assessed ($p < .001$). Further, the adolescent group scored significantly worse than the child group in Communication ($p < .001$) and Socialization ($p < .001$), however there were no differences for Daily Living Skills ($p = .148$). A summary of the results are displayed in Table 4 and illustrated in Figure 3.

Post-Hoc Analyses

Due to the substantial developmental changes that occur during the wide age range of children in the adolescent age group, the analyses were run for the adolescent group only, splitting the age group into two smaller age groups (10–12y) and (13–16y), excluding the child group. Our results for all three MANOVAs remained the same with no two-way or three-way interactions.

Discussion

The present study examined whether neuropsychological and behavioral impairments associated with prenatal alcohol exposure vary by age and sex. As expected, youth with prenatal alcohol exposure performed significantly worse than those without histories of exposure in all domains of neuropsychological and behavioral functioning. Contrary to our hypotheses, there were no significant interactions and no differences in performance between exposure groups based on age or sex. This finding remained robust when the older group was split into smaller, narrower age groups to account for changes related to developmental changes that occur between the ages of 10 and 16. Rather, main effects of age were found on neuropsychological performance and adaptive functioning, and main effects of sex were found on neuropsychological performance and psychopathology, regardless of exposure history.

Specific to age, older children in this study did not differ significantly from younger children on measures of psychopathology, but they were significantly worse than younger children in the Communication and Socialization domains of adaptive functioning. This was expected for the alcohol-exposed group but not for the control group. This finding is consistent with previous research addressing the CBCL syndrome scales (Steinhausen and Spohr, 1998) and adaptive functioning domains (Crocker et al., 2009, Streissguth et al., 1991, Thomas et al., 1998, Whaley et al., 2001) across different ages in children with FASD. While the reduction in scores from childhood to adolescence approaches clinical significance only for socialization, functionally, lower scores in socialization and communication may relate to increasing deficits in social skills in the population, which is consistent with previous reports (Crocker et al., 2009, Streissguth et al., 1991, Thomas et al., 1998, Whaley et al., 2001). For the control group, we expected no differences between the child and adolescent groups as the scores for both measures are normed for age. Inspecting the mean values for the adaptive behavior composites, it appears our control group was approximately one standard deviation above the mean for the child group and average for the adolescent group – leading to a main effect of age, though not clinically relevant. Regarding neuropsychological performance, the child group differed from the adolescent group on Verbal Similarities (child>adolescent) and Word Generation Semantic (child<adolescent). These isolated findings should not be over interpreted but appear to be driven by the performance of adolescent females, although mean scores for all groups were within the average range (see Supplemental Table). The lack of a group $\times$ age group interaction is in contrast to previous reports, which found that deficits in verbal executive functioning tasks worsened with age among children and adolescents with FASD (Rasmussen and Bisanz, 2009). These differences may be due to factors related to experimental design as the comparison to controls indicates a similar developmental trajectory in both groups.

Specific to sex, on adaptive functioning and the majority of behavioral scales, there was no difference between caregiver report for males or females, with the exception of somatic complaints where caregivers reported more somatic complaints for females than males. Further, females performed worse than males on some measures of neuropsychological functioning. Sex differences were not detected in the present study in the fluid reasoning and executive functioning or learning and memory domains, but females performed worse on a measure of visual-spatial ability (AW), and on one measure in the language domain (WD) across exposure history. While investigations of sexually dimorphic behavior using human subjects with FASD have been limited and we are hesitant to over interpret the current findings, our results are consistent with animal studies that found sexually dimorphic behaviors and abilities in rats with prenatal alcohol exposure follow a pattern similar to that of control rats (Otero and Kelly, 2012). Furthermore, many of the sexually dimorphic secondary disabilities in FASD, reviewed by Streissguth (2012), such as rates of confinement and school suspensions/expulsions, are also sexually dimorphic in the general population (Golinelli and Minton, 2014), which may help to explain why we did not see any interactions between exposure history and sex in the present study.

Clinically, the lack of interactions between age, sex, and exposure imply that children with prenatal alcohol exposure display similar neuropsychological and behavioral difficulties, regardless of age or sex, and may follow a developmental trajectory similar to that of

typically developing children, albeit at a lower performance level. As a result, youth with prenatal alcohol exposure may present with similar neuropsychological impairments and behavior problems, regardless of age or sex. This consistency improves the ability to accurately identify alcohol-affected individuals both in comparison to typical development and in comparison with other developmental disorders that are sexually dimorphic. Our post hoc analysis further supports this claim, as our results remained robust when the wider age range was divided into two smaller, more homogenous age groups. This also indicates that the deficits present in childhood for children with prenatal alcohol exposure are also present in adolescence, suggesting minimal improvement, but also no widening gap between performance and expectation.

Limitations and Suggestions for Future Research

While the current study has important clinical implications, the following limitations should be considered. First, the age ranges in each group were uneven and not continuous: child (5–7y) and adolescent (10–16y). Data was not collected from children ages 8–9y and as a result, the adolescent group included subjects from a wider developmental range. Due to the various cognitive, physiological and hormonal changes that occur during the late adolescent/early teen years, it could be argued that clinically relevant changes in neuropsychological functioning and behavior at this age may have gone undetected in this study. However, the post-hoc analyses tested for differences between younger and older adolescents in the 10–16y age group, and our results remained unchanged, thus supporting the inclusion of all adolescents in a single age group. Future studies would benefit from extending this investigation to adult populations to determine if the trends identified in the present study continue into adulthood. A second potential limitation of this study was the cross-sectional, rather than longitudinal, design. A longitudinal study would have included assessment scores from the same children at different time points and allowed us to detect changes in neuropsychological functioning and behavior within the same children over time. Given the additional possibility that neurocognitive testing may be less reliable at younger ages, future studies should consider a longitudinal design to confirm the current results.

Additional limitations of the current study include confounds that are inherent of the subject population and study design. For example, despite requests to refrain, some AE subjects needed to take medication on the day of testing due to the high prevalence of ADHD in the FASD population (Fryer et al., 2007, O'Malley and Nanson, 2002). While medication effects may have contributed to our results, excluding medicated children from our study would have decreased the generalizability of our results. Furthermore, the high prevalence of behavioral problems, such as disproportionate rates of ADHD, in the FASD population compared to typically developing children may have also contributed to our results (Fryer et al., 2007, O'Malley and Nanson, 2002). However, we recently assessed memory performance across the same age groups and found no age group differences in the alcohol-exposed group, suggesting no improvement with age, consistent with the current study. In that study, a group of non-exposed children with behavioral and developmental concerns was used as an additional control group and they did show improvement, with significantly higher scores in the adolescent group compared to the child group, indicating potential differential developmental trajectories and reducing the concern that the results are driven by

the disproportionate rates of psychopathology (Gross et al., 2016). Future studies should consider the inclusion of a similar clinical comparison group when examining behavioral deficits and other domains of neuropsychological impairments in the FASD population to extend these findings.

It is also possible that factors such as referral source and study design, diagnostic status, postnatal environmental factors, or reductions in general cognitive function may have influenced our results. The AE group is by and large a clinically-referred sample that was recruited retrospectively, though recruitment was broad-based. Our AE group also had a relatively large proportion of FAS cases (26.6%). It is possible that in this type of sample, neuropsychological and behavioral deficits are over-represented. However, the results were consistent with many previous studies that utilized a variety of recruitment methods. Further, within the AE group, we compared the GCA scores of individuals with and without FAS and found the subgroups to be clinically and statistically indistinguishable. Thus we feel that our results are representative of the larger population of youth with prenatal alcohol exposure.

In addition, while we included a measure of socioeconomic status in our analyses, other important environmental factors were not systematically incorporated. Factors such as exposure to violence or other trauma, home placement instability, access to appropriate nutrition, home literacy, and involvement with child protective services may all have important effects on child cognition and should be assessed in future studies. Lastly, it is possible that differences in IQ between the exposure groups may have contributed to our results. However, it is not appropriate to co-vary for IQ in research with a neurodevelopmental population and some of the subtests that make up the GCA were included as dependent variables in the analysis (Dennis et al., 2009). Further, it is notable that the average GCA score of the AE group in this study was in the low average range and thus, less likely than in previous studies to have a significant impact on results.

This study also has many strengths including the large, diverse sample size recruited from multiple geographical sites that promotes generalizability. Further, the wider developmental range and novel methodology of assessing the influence of age and sex allowed precise testing of these effects. Future studies should consider the impact of sex and age into other studies as there are continuing questions regarding the developmental trajectory of a variety of skills and functioning. A recent paper focused on identifying children affected by prenatal alcohol exposure was recently validated in both adolescent and child age groups (Goh et al., 2016), suggesting that there are not significant differences between these populations and emphasizing the need for early intervention. Further elucidation of how these demographic factors interact with the neuropsychological and behavioral abnormalities associated with FASD may contribute to better screening tools, improved accuracy of FASD diagnoses, and targeted interventions for individuals in high-risk subgroups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Performance of study groups on NEPSY-II Memory for Designs subtest, a representative neuropsychological measure. Data are presented as mean (+ SEM) scaled score (population mean = 10; SD = 3). Study subjects are male and female children (ages 5–7y) and adolescents (10–16y) in one of two groups: subjects with histories of prenatal alcohol exposure (AE), and typically developing controls (CON).

Figure 2.

Performance of study groups on CBCL Attention Problems scale, a representative psychopathology measure. Data are presented as mean (+ SEM) T-score (population mean = 50; SD = 10). Study subjects are male and female children (ages 5–7y) and adolescents (10–16y) in one of two groups: subjects with histories of prenatal alcohol exposure (AE), and typically developing controls (CON).

Figure 3.

Performance of study groups on VABS-II Daily Living Skills scale, a representative adaptive function measure. Data are presented as mean (+ SEM) scaled score (population mean = 10; SD = 3). Study subjects are male and female children (ages 5–7y) and adolescents (10–16y) in one of two groups: subjects with histories of prenatal alcohol exposure (AE), and typically developing controls (CON).

Table 1

Demographic data for subjects with histories of prenatal alcohol exposure (AE) and typically developing controls (CON)

Demographic Variable	AE						CON					
	Child (<i>n</i> = 69)			Adolescent (<i>n</i> = 123)			Child (<i>n</i> = 79)			Adolescent (<i>n</i> = 136)		
	M	F		M	F		M	F		M	F	
<i>n</i>	30	39		66	57		37	42		70	66	
Age [Mean (SD)]	6.66 (0.97)	6.75 (0.88)		13.05 (2.22)	13.14 (1.79)		6.55 (0.77)	6.41 (0.96)		13.82 (2.10)	13.57 (2.04)	
CIFASD Site [n (%)]												
Atlanta	18 (60.0)	12 (30.8)		14 (21.2)	11 (19.3)		6 (16.2)	16 (38.1)		13 (18.6)	17 (25.8)	
Los Angeles	0 (0.0)	0 (0.0)		10 (15.2)	7 (12.3)		1 (2.7)	0 (0.0)		10 (14.3)	12 (18.2)	
Minnesota	10 (33.3)	17 (43.6)		20 (30.3)	22 (38.6)		21 (56.8)	13 (31.0)		21 (30.0)	18 (27.3)	
San Diego	2 (6.7)	10 (25.6)		22 (33.3)	17 (29.8)		9 (24.3)	13 (31.0)		26 (37.1)	19 (28.8)	
Ethnicity [n (% Hispanic)]	5 (16.7)	2 (5.1)		9 (13.6)	11 (19.3)		8 (21.6)	6 (14.3)		12 (17.1)	17 (25.8)	
FAS [n (%)]	6 (20.0)	7 (17.9)		21 (31.8)	17 (29.8)		0 (0)	0 (0)		0 (0)	0 (0)	
GCA* [Mean (SD)]	85.03 (15.36)	91.11 (11.13)		91.12 (12.73)	86.30 (13.43)		107.00 (14.31)	102.34 (13.93)		107.20 (17.13)	100.08 (15.46)	
Handedness [n (% Right)]	24 (80.0)	30 (76.9)		57 (86.4)	52 (91.2)		34 (91.9)	40 (95.2)		61 (87.1)	59 (89.4)	
Race [n (% White)]	12 (40.0)	14 (35.9)		40 (60.6)	25 (43.9)		25 (67.6)	20 (47.6)		38 (54.3)	36 (54.5)	
SES [Mean (SD)]	46.04 (10.73)	43.19 (13.16)		45.88 (13.33)	46.74 (12.67)		52.48 (11.50)	47.88 (13.22)		46.63 (12.93)	45.94 (13.86)	

* Significant differences between exposure groups, $p < .05$

Note. CIFASD = Collaborative Initiative on Fetal Alcohol Spectrum Disorders, FAS = Fetal Alcohol Syndrome, GCA = General Cognitive Ability, SES = social economic status as measured by Hollingshead 4-Factor Index of Socioeconomic Status. SES scores range from 8–66, with higher scores indicating higher SES.

Table 2

Measures of neuropsychological function used in the current study

Domain	Assessment	Subtest	Description
Fluid Reasoning and Executive Functioning	NEPSY-II	Inhibition (INI)	Inhibitory control and impulsivity: measures child's ability to inhibit previously learned response
	DAS-II	Matrices (M)	Inductive reasoning: measures child's ability to identify, formulate, and test relationships between features in an abstract figure
	DAS-II	Sequential and Quantitative Reasoning (SQR)	Inductive reasoning: measures child's perception of sequential patterns in geometric figures and numerical relationships
Language	DAS-II	Verbal Similarities (VS)	Vocabulary and verbal development: measures a child's ability to identify common concept linking three words
	DAS-II	Word Definitions (WD)	Vocabulary knowledge: measures ability of child to define orally presented words
	NEPSY-II	Word Generation Semantic (WGS)	Language acquisition, retrieval, and verbal productivity
Learning and Memory	NEPSY-II	Memory for Designs Delayed (MDD)	Long-term storage and retrieval of visual-spatial information
	NEPSY-II	Memory for Faces Delayed (MFD)	Retention of encoded facial features
	NEPSY-II	Memory for Names Delayed (MND)	Long-term recall of previously learned names
	NEPSY-II	Narrative Memory Free Recall (NMF)	Immediate story recall
Visual-spatial Ability	DAS-II	Recall of Designs (RD)	Short-term visual recall: measures child's ability to recall and reproduce an abstract design
	DAS-II	Pattern Construction (PC)	Spatial ability: measures child's ability to copy a design with wooden blocks
	NEPSY-II	Arrows (AW)	Visuoperception: measures child's ability to judge line orientation

Note. DAS-II = Differential Abilities Scale, Second Edition

All DAS-II scores are T-Scores and all NEPSY-II scores are scaled scores.

Table 3

Parent-report measures of psychopathology and adaptive function used in the current study

Psychopathology: CBCL Syndrome Scales		Adaptive Functioning: VABS-II	
Domain	Subtest	Subtest	Description
Internalizing	Anxious/Depressed	Communication	Parent report of child's receptive, expressive, and written communication
	Withdrawn/Depressed		
	Somatic Complaints		
Mixed Syndrome	Social Problems [‡]	Daily Living Skills	Parent report of child's personal, domestic, and community skills
	Thought Problems [‡]		
	Attention Problems [‡]		
Externalizing	Rule-Breaking Behavior	Socialization	Parent report of child's interpersonal relationships, play, and coping skills
	Aggressive Behavior		

Note. CBCL = Child Behavior Checklist; VABS-II = Vineland Adaptive Behavior Scales – Second Edition

[‡] Denotes subtests that are not administered to children aged five and younger.

Table 4

Main and interaction effects of prenatal alcohol exposure, sex, and age on test performance on neuropsychological and behavioral measures

Neuropsychological Performance														
	Exposure		Age		Sex		Exposure × Age		Exposure × Sex		Age × Sex		Exposure × Age × Sex	
	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p
Main Effect:	< .001	.316	< .001	.135	< .001	.122	.264	.043	.174	.048	.634	.029	.583	.031
NEPSY-II MDD	< .001	.145	.361	.002	.531	.001	.425	.002	.739	< .001	.679	< .001	.322	.003
NEPSY-II MFD	< .001	.094	.275	.003	.194	.005	.746	< .001	.501	.001	.287	.003	.174	.005
NEPSY-II MND	< .001	.138	.724	< .001	.786	< .001	.312	.003	.034	.012	.671	< .001	.195	.005
NEPSY-II NMF	< .001	.098	.130	.006	.297	.003	.879	< .001	.532	.001	.522	.001	.521	.001
NEPSY-II INI	< .001	.112	.519	.001	.975	< .001	.117	.007	.020	.015	.525	.001	.322	.003
NEPSY-II AW	< .001	.151	.841	< .001	< .001	.079	.010	.018	.144	.006	.731	< .001	.509	.001
NEPSY-II WGS	< .001	.076	< .001	.045	.649	.001	.551	.001	.754	< .001	.390	.002	.852	< .001
DAS-II M	< .001	.100	.942	< .001	.292	.003	.597	.001	.181	.005	.207	.004	.499	.001
DAS-II SQR	< .001	.170	.812	< .001	.041	.011	.541	.001	.135	.006	.373	.002	.596	.001
DAS-II RD	< .001	.179	.652	.001	.056	.010	.926	< .001	.199	.004	.502	.001	.052	.010
DAS-II PC	< .001	.073	.442	.002	.114	.007	.676	< .001	.101	.007	.626	.001	.629	.001
DAS-II VS	< .001	.127	.001	.028	.068	.009	.338	.002	.465	.001	.073	.009	.446	.002
DAS-II WD	< .001	.107	.277	.003	.010	.018	.475	.001	.540	.001	.168	.005	.590	.001

Psychopathology														
	Exposure		Age		Sex		Exposure × Age		Exposure × Sex		Age × Sex		Exposure × Age × Sex	
	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p
Main Effect:	< .001	.546	.935	.009	.013	.054	.114	.037	.985	.005	.290	.027	.634	.017
Anxious/Depressed	< .001	.233	.562	.001	.181	.005	.055	.010	.734	< .001	.038	.012	.829	< .001
Withdrawn/Depressed	< .001	.193	.299	.003	.778	< .001	.114	.007	.833	< .001	.071	.009	.108	.007
Somatic Complaints	< .001	.164	.768	< .001	.023	.015	.677	< .001	.903	< .001	.518	.001	.271	.003
Social Problems	< .001	.397	.767	< .001	.582	.001	.479	.001	.643	.001	.338	.003	.751	< .001
Thought Problems	< .001	.380	.974	< .001	.518	.001	.915	< .001	.744	< .001	.137	.006	.381	.002
Attention Problems	< .001	.501	.619	.001	.163	.006	.181	.005	.540	.001	.074	.009	.384	.002

Psychopathology														
	Exposure		Age		Sex		Exposure × Age		Exposure × Sex		Age × Sex		Exposure × Age × Sex	
	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p
Rule-Breaking Behavior	< .001	.343	.617	.001	.896	.001	.887	< .001	.535	.001	.055	.010	.116	.007
Aggressive Behavior	< .001	.357	.526	.001	.481	.001	.828	< .001	.789	< .001	.044	.012	.427	.002
Adaptive Functioning														
	Exposure		Age		Sex		Exposure × Age		Exposure × Sex		Age × Sex		Exposure × Age × Sex	
	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p	<i>p</i>	η^2_p
Main Effect:	< .001	.450	< .001	.107	.347	.008	.806	.003	.026	.023	.666	.004	.233	.011
Communication	< .001	.417	< .001	.076	.160	.005	.928	< .001	.135	.006	.894	< .001	.057	.009
Daily Living Skills	< .001	.313	.148	.005	.272	.003	.504	.001	.322	.003	.835	< .001	.510	.001
Socialization	< .001	.375	< .001	.040	.893	< .001	.465	.001	.868	< .001	.310	.003	.363	.002

Note. CBCL = Child Behavior Checklist; MDD = Memory for Designs Delayed; MFD = Memory for Faces Delayed; NMF = Narrative Memory Free Recall; INI = Inhibition; AW = Arrows; WGS = Word Generation Semantic; DAS-II = Differential Abilities Scales, Second Edition; M = Matrices; SQR = Sequential and Quantitative Reasoning; RD = Recall of Designs; PC = Pattern Construction; VS = Verbal Similarities; WD = Word Definitions; VABS-II = Vineland Adaptive Behavior Scales, Second Edition; η_p^2 = Partial eta squared effect size; $p < .017$ = significant with Bonferroni correction; significant findings are bolded