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Effects of Prenatal Alcohol Exposure and ADHD on Adaptive Functioning

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Abstract

Background—Heavy prenatal alcohol exposure and attention-deficit/hyperactivity disorder (ADHD) are associated with adaptive behavior deficits. The present study examined the interaction between these two factors on parent ratings of adaptive behavior.

Methods—As part of a multisite study, primary caregivers of 317 children (8–16y, M=12.38) completed the Vineland Adaptive Behavior Scales-II (VABS-II). Four groups of subjects were included: children with prenatal alcohol exposure with (AE+, $n = 82$) and without ADHD (AE–, $n = 34$), children with ADHD (ADHD, $n = 71$), and control children (CON, $n = 130$). VABS-II

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*The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD; E. Riley, San Diego State University, Principal Investigator) includes 16 different centers where data collection and analysis take place. The data collection sites and associated investigators described in this paper are: San Diego State University (S.N. Mattson), the University of New Mexico and Northern Plains (P.A. May, W.O. Kalberg), University of California, Los Angeles (E.R. Sowell) and Emory University (C.A. Coles and J.A. Kable).

domain scores (Communication, Daily Living Skills, Socialization) were examined using separate 2 (Alcohol Exposure [AE]) \times 2 (ADHD diagnosis) between-subjects ANCOVAs.

Results—There were significant main effects of AE ($p < .001$) and ADHD ($p < .001$) on all VABS-II domains; alcohol-exposed children had lower scores than children without prenatal alcohol exposure and children with ADHD had lower scores than those without ADHD. There was a significant AE \times ADHD interaction effect for Communication [$F(1, 308) = 7.49, p = .007$, partial $\eta^2 = .024$], but not Daily Living Skills or Socialization domains ($ps > .27$). Follow up analyses in the Communication domain indicated the effects of ADHD were stronger in comparison subjects (ADHD vs. CON) than exposed subjects (AE+ vs. AE-) and the effects of alcohol exposure were stronger in subjects without ADHD (AE- vs. CON) than in subjects with ADHD (AE+ vs. ADHD).

Conclusion—As found previously, both prenatal alcohol exposure and ADHD increase adaptive behavior deficits in all domains. However, these two factors interact to cause the greatest impairment in children with both prenatal alcohol exposure and ADHD for communication abilities. These results further demonstrate the deleterious effects of prenatal alcohol exposure and broadens our understanding of how ADHD exacerbates behavioral outcomes in this population.

Keywords

Adaptive behavior; fetal alcohol syndrome (FAS); fetal alcohol spectrum disorders (FASD); attention-deficit/hyperactivity disorder (ADHD)

Introduction

Heavy prenatal alcohol exposure is a leading preventable cause of developmental disorders and mental retardation (American Academy of Pediatrics Committee on Substance Abuse and Committee on Children With Disabilities, 2000). A subset of children with histories of heavy prenatal alcohol exposure meet the diagnostic criteria for fetal alcohol syndrome (FAS), which is diagnosed in the presence of craniofacial anomalies, growth deficiency, and central nervous system dysfunction (Bertrand et al., 2005; Hoyme et al., 2005; Jones and Smith, 1973; Stratton et al., 1996). Although the majority of children with histories of heavy prenatal alcohol exposure do not exhibit the distinguishing craniofacial features associated with FAS (Bertrand et al., 2005; Sampson et al., 1997), they do exhibit similar neurobehavioral impairments as those with FAS (for review, see Mattson et al., 2011; Mattson and Riley, 1998). Fetal alcohol spectrum disorders (FASD) encompass the full range of impairments resulting from prenatal alcohol exposure, including FAS. Prevalence rates are estimated at 0.2–0.7% for FAS and 2–5% for FASD (May et al., 2009).

Deficits in adaptive function, which encompass the ability to monitor and adjust behavior in changing environments (Sparrow et al., 1984), are consistently documented in this population (Crocker et al., 2009; Fagerlund et al., 2012; Thomas et al., 1998; Ware et al., 2012). Children with prenatal alcohol exposure demonstrate low emotional maturity, poor interpersonal and communication skills, and are rated by parents and teachers as having poorer social skills than non-exposed peers (Crocker et al., 2009; Fagerlund et al., 2012; McGee et al., 2008; Schonfeld et al., 2005). These impairments may lead to secondary

disabilities such as academic failure, increased delinquency, and dependent living in adulthood (Howell et al., 2006; Spohr et al., 2007; Streissguth et al., 2004). Adaptive deficits begin early, become more severe with age (Crocker et al., 2009; Fagerlund et al., 2012), and are not accounted for by overall intellectual impairments (Fagerlund et al., 2012).

Attention-deficit/hyperactivity disorder (ADHD) has a high co-occurrence in FASD, with prevalence estimates consistently over 60% (Fryer et al., 2007; Steinhausen et al., 1993). Given high clinical overlap between these two conditions, including the presence of adaptive deficits (Crocker et al., 2009), recent research has focused on distinguishing children with prenatal alcohol exposure and non-exposed children with ADHD (e.g., Crocker et al., 2011; Vaurio et al., 2011). Despite many similarities, differences between these clinical populations have been documented in neuropsychological domains including attention, executive functioning, and mathematical processing (for review, see Mattson et al., 2011). Furthermore, prenatal alcohol exposure may be associated with more than one behavioral phenotype resulting from a concomitant ADHD diagnosis.

Recent behavioral studies have distinguished children with co-occurring prenatal alcohol exposure and ADHD from alcohol-exposed children without ADHD; children with both disorders have greater behavioral and psychiatric problems than alcohol-exposed children without ADHD (Graham et al., 2013; Ware et al., 2013). One study (Graham et al., 2013) examined whether an ADHD diagnosis worsened the effect of prenatal alcohol exposure on symptoms of sluggish cognitive tempo (SCT), which is characterized by varying alertness and orientation, sluggishness, under activity, and apparent daydreaming (McBurnett et al., 2001). Results indicated that children with both ADHD and prenatal alcohol exposure had elevated SCT symptoms relative to alcohol-exposed children without ADHD. However, alcohol-exposed children with ADHD did not differ from children with only ADHD. Another study (Ware et al., 2013) examined the effects of ADHD and prenatal alcohol exposure on behavioral problems and psychiatric comorbidity and found an exacerbated effect of having both disorders on behavioral problems, particularly externalizing disorders (i.e., conduct disorder). A third study examined the relation between executive function and parent-reported adaptive behavior in children with ADHD and children with prenatal alcohol exposure. While the interaction between alcohol exposure and ADHD was not examined, a post hoc analysis indicated greater adaptive dysfunction in alcohol-exposed children with ADHD compared to alcohol-exposed children without ADHD (Ware et al., 2012). Together these studies suggest that parents report greater behavioral problems in children who have both prenatal alcohol exposure and ADHD than alcohol-exposed children without ADHD, despite elevations in both groups compared to non-exposed controls. Exacerbated outcomes associated with co-occurring ADHD and heavy prenatal alcohol exposure may be specific to parent reports of behavior, as a recent study found no differences between children with heavy prenatal alcohol exposure with and without ADHD on performance-based neuropsychological measures of executive function and general intelligence (Glass et al., 2013b).

Given such findings, research addressing the combined effect of prenatal alcohol exposure and ADHD on children's adaptive ability is necessary in refining the neurobehavioral profile of prenatal alcohol exposure and enhancing diagnostic identification. Previous studies have

indicated that adaptive behavior of children with FASD differs from that of non-exposed children with ADHD (Crocker et al., 2009), but the interaction between these two conditions has not been studied. The current investigation sought to determine whether previously documented behavioral differences in alcohol-exposed children with or without ADHD extend to parent measures of adaptive behavior. Four groups of children were studied: (i) children with prenatal alcohol exposure with ADHD, (ii) children with prenatal alcohol exposure without ADHD, (iii) children with ADHD, and (iv) controls. We expected there to be an interactive effect of ADHD and prenatal alcohol exposure on all adaptive domains, whereby children with both disorders would show the greatest impairments and all clinical groups would exhibit adaptive deficits compared to control children without ADHD.

Methods

General Methods

Children ($N = 317$) between the ages of 8–16 years ($M = 12.38$, $SD = 2.52$) were recruited for an ongoing multisite study conducted by the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) (Mattson et al., 2010). Standardized testing took place at five testing locations: Center for Behavioral Teratology at San Diego State University; The Fetal Alcohol and Drug Exposure Clinic at Emory University; Center on Alcoholism, Substance Abuse and Addictions at the University of New Mexico; seven communities throughout North Dakota, South Dakota, and Montana (Northern Plains); and the Fetal Alcohol and Related Disorders Clinic at the University of California, Los Angeles. Though CIFASD is an international study, only data from the U.S. testing centers were considered in these analyses to decrease potential cultural and societal influences on adaptive behavior.

As part of CIFASD, subjects at all testing sites underwent the same standardized neuropsychological battery in a single day by a trained examiner, blind to subject group. As part of this battery, general intelligence was estimated using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV, Wechsler, 2004) and primary caregivers completed select modules of the clinician-assisted National Institute of Mental Health Diagnostic Interview Schedule for Children IV (C-DISC-4.0, Shaffer et al., 2000) along with behavioral reports and questionnaires including the Vineland Adaptive Behavior Scales-II (VABS-II, Sparrow et al., 2005). Informed consent and assent were obtained from all subjects and their legal guardians prior to testing and the Institutional Review Boards at each CIFASD site approved this study. Subjects and their parents were provided with a financial incentive to participate.

Subjects

Subjects were recruited through various modalities, including community outreach, advertising, and word of mouth. Children with prenatal alcohol exposure had confirmed histories of heavy prenatal exposure to alcohol, defined as *in utero* exposure to an average of 14 drinks per week or 4 alcoholic drinks per occasion at least once per week during gestation. Prenatal exposure to alcohol was confirmed retrospectively through medical history, birth records, social services records, and maternal report and questionnaires, when available. In many cases, precise measures of alcohol consumption were unavailable. In

these cases, mothers were reported to be “alcoholic” or alcohol abusing or dependent during pregnancy. In order to determine alcohol-related diagnoses, a member of the CIFASD Dismorphology Core evaluated each study subject using a standardized assessment following the CIFASD Dismorphology Core diagnostic criteria, which have been published elsewhere (Jones et al., 2006; Mattson et al., 2010). For the purposes of this research project, a diagnosis of FAS was based on physical features and did not consider neurobehavioral criteria. Of the children in the alcohol-exposed groups, 32 (27.6%) met these research criteria for FAS. Children with prenatal alcohol exposure were divided into two groups: those meeting DSM-IV criteria for ADHD per the C-DISC-4.0 (AE+; $n = 82$) and those who did not meet criteria for ADHD (AE-; $n = 34$) (American Psychiatric Association, 2000). Children were excluded from all groups if they demonstrated subclinical symptoms of ADHD (i.e., 4 or 5 ADHD symptoms on the C-DISC-4.0).

Comparison children with and without ADHD were recruited from the community using similar methods and had no prenatal alcohol exposure or minimal exposure (i.e., no more than 1 drink per week on average and never more than 2 drinks per occasion). Additional information regarding the recruitment of the CON and ADHD groups can be found in Mattson et al., 2010. The ADHD group ($n = 71$) consisted of children who met DSM-IV diagnostic criteria for ADHD per the C-DISC-4.0. The CON group ($n = 130$) consisted of children who did not meet diagnostic or subclinical criteria for ADHD. General exclusionary criteria for all groups were: non-fluent English speaker, history of significant head injury or loss of consciousness > 30 minutes, adopted from abroad after the age of 5 years old or < 2 years before assessment, or psychiatric (e.g., psychosis) or physical disability that prevented successful study completion. While CIFASD procedures were set in place prior to the publication of DSM-5, ADHD diagnostic criteria for children as defined by the DSM-IV are unchanged in the DSM-5 (American Psychiatric Association, 2013). Typically approximately 40–45% of alcohol-exposed and ADHD subjects in our studies routinely take medication for ADHD (Glass et al., 2013a). Subjects are not excluded from participation based on medication usage given the potential limitation to the generalizability of results as well as ethical implications in subject selection.

Measures

Vineland Adaptive Behavior Scales-II (VABS-II)—The VABS-II Parent/Caregiver Rating Form (Sparrow et al., 2005) is a standardized parent questionnaire assessing adaptive behavior. Behavioral questions are scored as 0 (*never*), 1 (*sometimes or partially*), or 2 (*usually*). The measure provides a standard adaptive composite score (population $M = 100$, $SD = 15$), which is derived from three standardized and age-normed domain scores: Communication, Socialization, and Daily Living Skills. Computerized scoring software was used to derive standardized adaptive scores. The VABS-II is a valid and reliable measure of adaptive functioning in multiple neurodevelopmental populations, including ADHD (Perry and Factor, 1989; Sparrow et al., 2005).

Computerized Diagnostic Interview Schedule for Children IV (C-DISC-4.0)—The C-DISC-4.0 is a computerized clinician-assisted structured diagnostic instrument based on the DSM-IV (American Psychiatric Association, 2000; Shaffer et al., 2000) that assesses

the presence of psychiatric diagnoses, including ADHD, as defined by the DSM-IV by evaluating clinical symptoms experienced by their child during the past *month*, *six months*, *year*, and *whole life*. For the purposes of this research study, diagnoses were derived via computerized algorithms, and the symptoms over the past six months were used to designate a positive ADHD diagnosis. The C-DISC-4.0 was administered in a single 60–120 minute session at the time of testing.

Data Analysis

Statistical analyses were conducted using the SPSS statistical package version 19.0 (SPSS, 2010). Demographic data were analyzed using chi-square test for independence (sex, race, ethnicity, and handedness) and standard analysis of variance (ANOVA; age and FSIQ). Pairwise comparisons (Tukey's Honestly Significant Difference [HSD] test) were used to follow up any significant group differences.

Similar to our recent study on neuropsychological findings (Glass et al., 2013b), two alternative analytic strategies were planned prior to data analysis: (1) if the alcohol-exposed groups (AE+ and AE-) *differed*, based on initial single-sample *t*-tests for each adaptive domain score (Communication, Socialization, and Daily Living Skills), domain scores would be analyzed using three separate 2×2 (AE \times ADHD diagnosis) between-subjects analysis of covariance (ANCOVA) tests using an alpha level of $p=.05$. Significant interactions would be followed-up using simple effects tests with an alpha per test rate of .0125 (.05/4) using Bonferroni correction to protect against Type-I error; (2) if the alcohol-exposed groups *did not differ* on initial comparison, these groups would be combined into a single alcohol-exposed group (AE+/-) and compared with the ADHD and CON groups in three separate univariate ANCOVAs. Significant group differences would be followed up using Tukey's HSD for pairwise analysis. For all analyses, demographic variables were considered as covariates if they were significantly ($p < .05$) correlated with VABS-II domain scores. Preliminary analyses revealed that site was not significantly associated with VABS-II domain scores, with the exception of Daily Living Skills scores. Furthermore, none of the three-way interactions between site, ADHD, and exposure histories were significant for any domain scores. Data by group and site are presented in the supplemental table. Despite expected group differences on IQ, this variable was not considered to be an appropriate covariate in these analyses given theoretical and statistical arguments against covarying IQ in neurodevelopmental disorders (Dennis et al., 2009).

Results

Demographic Data

Demographic data and statistics are presented in Table 1. Groups were similar on handedness, race, and age. However, groups differed on ethnicity, sex, and, as expected, Full Scale IQ (FSIQ). For ethnicity, the AE+ group had fewer Hispanic subjects compared to the ADHD group, which did not differ from the AE- or CON groups. The ADHD group had more male subjects relative to the AE- and CON groups, which did not differ from each other or the AE+ group. The ADHD and AE+ groups had similar number of male subjects.

On FSIQ, the AE+ group had lower scores than the AE– and ADHD groups, which were similar. All clinical groups had lower FSIQ compared to the CON group.

Analyses of Adaptive Behavior Data

Average adaptive behavior scores for the 4 groups are presented in Table 2. Individual domain scores were missing for 5 subjects in the AE+ group, 1 subject in the AE– group, 2 subjects in the ADHD group, and 5 subjects in the CON group. The AE+ group had significantly lower scores than the AE– group for all three domains: Communication, $t(112) = 3.92, p < .001$, Daily Living Skills, $t(110) = 3.86, p < .001$, and Socialization, $t(112) = 5.21, p < .001$. Given that the AE+ and AE– groups differed significantly, the first analytic strategy was employed. Age, sex, race, and ethnicity were tested as covariates. Age was significantly ($p < .05$) negatively correlated with all three domain scores. Domain scores were also significantly related to sex (Daily Living Skills, Socialization) and race (Communication, Socialization). However, when sex was included as a covariate in the analysis of the Daily Living Skills and Socialization scores, it was not significant and was dropped from the final analyses. Similarly, when race was included in the Communication analysis, it was not significant and was not included in subsequent analyses of this domain. Therefore, race was included in analyses of the Socialization domain and age was included in all analyses.

Communication Domain—ANCOVA results are detailed in Table 2. These analyses revealed significant main effects of AE and ADHD diagnosis on Communication domain scores; both factors led to lower scores. Age was a significant ($p = .001$) covariate. The AE \times ADHD interaction was statistically significant. The effect of ADHD diagnosis was examined at each level of AE for the Communication domain. For children with prenatal alcohol exposure, the AE+ group had significantly lower Communication scores than the AE– group ($p < 0.001$). For comparison children, the ADHD group had significantly lower Communication scores compared to the CON group ($p < 0.001$). The effect of AE was then examined at each level of ADHD diagnosis for Communication scores. The AE+ group had significantly lower communication scores than the ADHD group ($p < 0.001$). Similarly, for children without ADHD, the AE– group had significantly lower communication scores than the CON group ($p = 0.001$).

To further examine the interaction, effect sizes for the relevant contrasts were compared (Konstantopoulos and Hedges, 2009). The effect size (Cohen's $d = 1.47$) for the ADHD vs. CON contrast was significantly greater than the effect size (Cohen's $d = 0.80$) for the AE+ vs. AE– contrast (95% confidence interval [CI] around the difference between the two effect sizes = 0.15–1.20) indicating that the effect of ADHD was stronger in the comparison subjects than in those with prenatal alcohol exposure. Similarly, the effect size (Cohen's $d = 1.33$) for the AE– vs. CON contrast was significantly greater than the effect size (Cohen's $d = 0.66$) for the AE+ vs. ADHD contrast (95% CI = 0.15–1.19) indicating that the effect of alcohol exposure was stronger in the subjects without ADHD than in those with ADHD. In sum, results indicate that the effects of ADHD and prenatal alcohol-exposure are not uniform: ADHD affects children with minimal or no prenatal alcohol exposure more than

children with prenatal alcohol exposure and prenatal alcohol exposure affects children without ADHD more than children with ADHD.

Daily Living Skills Domain—ANCOVA results (see Table 2) revealed significant main effects of AE and ADHD diagnosis on Daily Living Skills domain scores; both factors led to lower scores. Age was a significant ($p = .001$) covariate. The AE \times ADHD interaction was not significant.

Socialization Domain—ANCOVA results (see Table 2) revealed significant main effects of AE and ADHD diagnosis on Socialization domain scores; both factors led to lower scores. Age ($p = .015$) and race ($p = .004$) were significant covariates. The AE \times ADHD interaction was not significant.

Post Hoc Comparison of Alcohol-Exposed Subjects With and Without FAS

To determine whether the results described above were related to the presence of an FAS diagnosis, domain scores for the alcohol-exposed subjects were re-analyzed using separate 2 (FAS) \times 2 (ADHD) ANOVAs. For all three adaptive domains there was a significant main effect of ADHD ($ps = .002$), but no significant main effect of FAS ($ps > .19$) or FAS \times ADHD interactions ($ps > .31$). Therefore, alcohol-exposed children with ADHD, regardless of FAS diagnosis, had poorer adaptive behavior than alcohol exposed subjects without ADHD.

Discussion

Children with histories of heavy prenatal alcohol exposure and children with ADHD exhibit adaptive behavior deficits, affecting social, communication, and independent living abilities (Carr et al., 2010; Crocker et al., 2009; Steinhausen et al., 1993; Thomas et al., 1998; Whaley et al., 2001). The current study examined the interaction between prenatal alcohol exposure and ADHD on parent-rated adaptive behavior in four groups: children with prenatal alcohol exposure and ADHD (AE+), children with prenatal alcohol exposure without ADHD (AE-), children with ADHD (ADHD), and control children (CON). As expected, children with both prenatal alcohol exposure and ADHD had significantly lower adaptive scores than alcohol-exposed children without an ADHD diagnosis, which supports earlier findings of behavioral differences between these groups (Graham et al., 2013; Ware et al., 2013). Results also support previous independent reports of adaptive deficits associated with prenatal alcohol exposure (Crocker et al., 2009; Fagerlund et al., 2012; Streissguth et al., 1996; Ware et al., 2012) and ADHD (Barkley et al., 2006; Barkley et al., 2002; Crocker et al., 2009; Stavro et al., 2007).

This is the first study to examine whether an ADHD diagnosis worsens parent-reported adaptive scores in alcohol-exposed children and whether this effect is greater than in comparison children. As expected, children with both heavy prenatal alcohol exposure and ADHD had significantly worse adaptive scores on all three domains relative to alcohol-exposed children without ADHD. However, the significant interaction between ADHD and prenatal alcohol exposure was significant only for the Communication domain. Unlike previous findings (e.g., Ware et al., 2013) and our expectations, the significant interaction

was driven by the greater magnitude of ADHD-related deficits in comparison children (the ADHD vs. CON comparison) as opposed to a synergistic effect of ADHD and prenatal alcohol exposure on behavior in children. These findings are similar to our recent neuropsychological study (Glass et al., 2013b). One interpretation of these results is that the effect of ADHD on communication skills is outweighed by the effect of prenatal alcohol exposure. Although there is an exacerbated effect when both ADHD and alcohol exposure are present, the magnitude of the difference between the alcohol-exposed subjects and controls indicates a larger effect of alcohol exposure than ADHD on adaptive behavior in general and communication skills, specifically.

Results for the Daily Living Skills and Socialization domain scores suggest that children with histories of heavy prenatal alcohol exposure and ADHD may have difficulty completing age-appropriate self-care, managing money, going places independently, observing rules, picking up on social cues, and avoiding risk social situations. These deficits could, in turn, lead to additional secondary deficits including reduced vocational success. The non-significant AE×ADHD interaction terms suggest that ADHD-related deficits on these domains are similar for exposed and comparison children: having ADHD lowered scores by approximately 1 SD in both exposed and comparison children. This differs from what we had originally hypothesized for these domains. In a previous study of an independent sample, socialization and communication deficits were similar in children with prenatal alcohol exposure (all with ADHD) and comparison children with ADHD whereas daily living deficits were significantly worse in the alcohol-exposed group (Crocker et al., 2009). In the current study, although greater deficits were seen in the AE+ group than the AE- group, the effect of ADHD did not differ from that seen in the comparison samples (ADHD vs. CON) suggesting that alcohol-exposed children may benefit from interventions designed for ADHD in these domains.

Findings from the Communication domain indicate that parents of children with prenatal alcohol exposure and ADHD (the AE+ group) reported greater difficulties communicating needs, conveying important information, and reporting detailed accounts of past events compared to parents of children with either prenatal alcohol exposure or ADHD. Since prenatal alcohol exposure, regardless of ADHD diagnosis, is associated with an impaired ability to produce contextually driven dialogue and provide sufficient organization and information during narrative stories (Aragón et al., 2008; Coggins et al., 2007; McGee et al., 2009), the added presence of ADHD, which is independently associated with similar impairments (Bruce et al., 2006), may place children at greater risk for academic and occupational failure and poorer interpersonal relationships (McGee and Riley, 2007; Schonfeld et al., 2005; Streissguth et al., 2004).

Alcohol-exposed children without ADHD and comparison children with ADHD were similar in terms of mean adaptive behavior scores, which differs from previous studies of behavior (e.g., Graham et al., 2013). Greater examination into how these two clinical groups differ, both behaviorally and cognitively, may aid in improved identification of alcohol-exposed children. The significant difference between AE+ and AE- on all parent-reported scores differs from recent neuropsychological findings of similar performance between alcohol-exposed children with and without ADHD on performance-based measures of

intellectual and executive functioning (Glass et al., 2013b). It is also possible that parent reports may differentially support cognitive performance in this population. In a recent study, we demonstrated closer correspondence of parent reports and laboratory measures for attention than for hyperactivity for alcohol-exposed children (Glass et al., 2013a). The combination of these results with the current study support the need to consider parent reports of behavior in addition to performance-based outcomes, as echoed by the DSM-5, which advocates multi-method evaluations and assessments of diagnoses (American Psychiatric Association, 2013). While cognitive outcomes as measured through performance-based laboratory measures may indicate a similar neuropsychological profile regardless of ADHD, parents of children with prenatal alcohol exposure describe their child as having greater behavioral deficits in the presence of an ADHD diagnosis.

Limitations

One limitation of the current study is the use of parent questionnaires, which are not a directly quantitative measure of adaptive functioning. Parent questionnaires may reflect increased subjectivity of a child's adaptive functioning and parent/caregiver expectations of daily functioning may differ in the clinical groups compared to controls (McGee et al., 2008; Streissguth et al., 2004), although this relation has not been examined empirically. Additional study using an ecologically-valid, objective measure of adaptive behavior would support the current findings.

Our use of a dichotomous ADHD variable may not be representative of all children with prenatal alcohol exposure. Since children with intermediate or subclinical symptoms of ADHD were excluded from the study, these results are not generalizable to the entire population of children with prenatal alcohol exposure. Therefore, future investigations of behavioral deficits in children with prenatal alcohol exposure would benefit from utilizing a continuous ADHD measure, allowing for a more thorough examination of the degree to which ADHD symptomology or subtype differences affect behavioral outcomes. Additionally, comorbid psychiatric disorders were not assessed in the current analysis. It is possible that parent-reported behavioral problems differ significantly in the presence of additional psychiatric pathology, which is common in children with histories of heavy prenatal alcohol exposure (Fryer et al., 2007; Ware et al., 2013). Similarly, our analytic strategy may have affected the reporting of results. We used a 2×2 design and the lack of a significant interaction for the Socialization and Daily Living Skills domains precluded follow-up group comparisons. While the results appear somewhat consistent across domains, closer examination reveals that differences between the AE+ and AE- groups are smaller for Communication than for Daily Living Skills and Socialization while the differences between the ADHD and CON groups are larger for Communication than for Daily Living Skills and Socialization. In addition, differences in variability across both group and domain could have affected these results.

Additionally, demographic variables related to adaptive functioning, such as socioeconomic status (SES) and home environment and placement, were not examined in the current analyses, as data were not available for all subjects who participated in CIFASD. In non-exposed children, low SES is associated with ADHD severity (Freitag et al., 2012; Pressman

et al., 2006), school-readiness, behavioral problems, and social development in children (National Institute of Child Health and Human Development Early Child Care Research Network, 2005). Children with prenatal alcohol exposure are more likely than non-exposed children with ADHD and controls to live with non-biological caregivers and, therefore, may represent a population at risk for behavioral deficits in general (Fagerlund et al., 2011). In the CIFASD sample, more of our alcohol-exposed subjects are in foster or adoptive care (61% of our exposed sample) than subjects in the comparison groups (9% of our comparison sample) (Ware et al., 2013). However, the subjects in foster/adoptive care have had relatively stable placements (current placement >2 years on average) and thus, caregivers know them well enough to respond accurately. Home placement is also shown to impact secondary disabilities, including adaptive functioning in children with prenatal alcohol exposure (Coggins et al., 2007; Fagerlund et al., 2012; Paley et al., 2006; Streissguth et al., 2004) and children with ADHD (Freitag et al., 2012; Pressman et al., 2006; Wells et al., 2000). Given these findings, future research should continue to investigate the role of home environment and SES on neurobehavioral outcomes in prenatal alcohol exposure. Additionally, we did not examine or correct for the relation between adaptive behavior and IQ score, thus we cannot rule out the added effect of lowered IQ. However, given that lowered IQ is an intrinsic feature of prenatal alcohol exposure, covarying for IQ in analyses would substantially reduce variance and create statistically overcorrected results, as well as decrease the generalizability of the current findings (Dennis et al., 2009). Finally, differences in medication usage may have influenced our results. Ethical and methodological factors prohibited our inclusion of only medication-naïve or unmedicated subjects.

Strengths

Despite noted limitations the current study has several strengths, including the large sample size and sample representativeness; the alcohol-exposed groups included 32 children (27.8%) with FAS and had an average IQ score of 84. This large sample allowed us to examine prenatal alcohol exposure and ADHD as independent factors. Moreover, the current study design, which included multiple testing locations across the United States, reflects a wide population base that may offer more reliable and stable generalizations of these findings to children with prenatal alcohol exposure in the U.S.

Implications and future directions

Our results indicate that, from a caregiver standpoint, children with co-occurring prenatal alcohol exposure and ADHD may require more integrative supportive services to improve adaptive abilities than children with only prenatal alcohol exposure. The results also indicate that the effect of ADHD differs in alcohol-exposed and comparison children and across adaptive domains. Understanding behavioral phenotype differences in FASD is paramount to developing both behavioral and psychopharmacological interventions for individuals across the spectrum. To date, only a few behavioral intervention studies have been administered to children with prenatal alcohol exposure (for review, see Peardon et al., 2009). Current and previous (Graham et al., 2013; Ware et al., 2013) findings indicate that the presence of ADHD may mediate treatment outcomes in children with prenatal alcohol exposure; behavioral interventions may need to be tailored towards alcohol-exposed

children with or without ADHD, as discrete behavioral phenotypes associated with an ADHD diagnosis suggests the need to treat these two groups differently. For example, a focus on communication skills, which has been examined in younger children with prenatal alcohol exposure (cf. Adnams et al., 2007), may be more beneficial for alcohol-exposed children with ADHD than children with either alcohol exposure or ADHD alone, whereas interventions focused on daily living skills and socialization shown to benefit children with ADHD could be adapted for children with prenatal alcohol exposure, regardless of ADHD status.

In conclusion, the current results broaden our understanding of the effects of heavy prenatal alcohol exposure and specifically how co-occurring ADHD influences behavior in this population. Further research is needed to increase understanding of how disparate behavioral phenotypes resulting from prenatal alcohol exposure affect behavioral and neuropsychological outcomes in order to: (i) increase sensitivity and specificity of the clinically-relevant neurobehavioral profile associated with prenatal alcohol exposure, (ii) promote accurate differential diagnosis between children with prenatal alcohol exposure and other clinical populations, and (iii) develop and implement more effective interventions for alcohol-exposed individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Demographic data for children with prenatal alcohol exposure and ADHD (AE+), prenatal alcohol exposure without ADHD (AE-), children with ADHD (ADHD), and control children (CON).

Table 1

| Demographic Variable | AE+ (n = 82) | AE- (n = 34) | ADHD (n = 71) | CON (n = 130) | Omnibus Statistic | p-value |
|---|---------------|---------------|---------------|----------------|--------------------------|---------|
| CIFASD Site [N (%)] | | | | | | |
| Atlanta | 15 (18.3) | 12 (35.3) | 18 (25.4) | 19 (14.6) | | |
| Los Angeles | 15 (18.3) | 8 (23.5) | 1 (1.4) | 17 (13.1) | | |
| Northern Plains States | 11 (13.4) | 4 (11.8) | 7 (9.9) | 17 (13.1) | | |
| Albuquerque | 5 (6.1) | 2 (5.9) | 10 (14.1) | 18 (13.8) | | |
| San Diego | 36 (43.9) | 8 (23.5) | 35 (49.3) | 59 (45.4) | | |
| Handedness [N (% Right)] | 72 (87.8) | 31 (91.2) | 63 (88.7) | 121 (93.1) | $\chi^2 (df=3) = 1.98$ | .577 |
| FAS [N (%)] | 22 (26.8) | 10 (29.4) | 0 (0) | 0 (0) | | |
| Sex [N (% Males)] | 52 (63.4) | 15 (44.1) | 53 (74.6) | 71 (54.6) | $\chi^2 (df=3) = 11.91$ | .008 |
| Race [N (%White)]¹ | 52 (63.4) | 13 (38.2) | 46 (64.8) | 91 (70.0) | $\chi^2 (df=18) = 26.93$ | .080 |
| Ethnicity [N (% Hispanic)]² | 6 (7.3) | 6 (17.6) | 19 (26.8) | 24 (18.5) | $\chi^2 (df=6) = 13.68$ | .033 |
| Age [M (SD)] | 12.54 (2.39) | 12.66 (2.57) | 11.83 (2.52) | 12.51 (2.58) | $F (3, 313) = 1.49$ | .216 |
| FSIQ [M (SD)]³ | 82.42 (17.35) | 88.88 (14.25) | 91.80 (18.44) | 110.67 (11.88) | $F (3, 311) = 65.33$ | < .001 |

¹ Race was analyzed using NIH-designated categories: American Indian/Alaska Native, Asian, Black or African American, White, More than one Race, Other, Unknown/Not Specified

² Ethnicity was missing for 7 subjects

³ FSIQ was missing for 2 subjects

Table 2

Mean domain scores on the Vineland Adaptive Behavior Scales-II (VABS-II) for children with prenatal alcohol exposure and ADHD (AE+), prenatal alcohol exposure without ADHD (AE-), children with ADHD (ADHD), control children (CON).

| VABS-II Domain ^{1,2} | AE+ | | AE- | | ADHD | | CON | | Main Effect of AE | | | Main Effect of ADHD | | | AE × ADHD Interaction | | |
|----------------------------------|-------|-------|-------|--------|------|----|-----|----|---------------------|---------|------------------|---------------------|---------|------------------|-----------------------|---------|------------------|
| | M | SD | M | SD | M | SD | M | SD | F-value | p-value | partial η^2 | F-value | p-value | partial η^2 | F-value | p-value | partial η^2 |
| Communication | | | | | | | | | | | | | | | | | |
| M | 79.28 | 91.06 | 88.93 | 110.05 | | | | | | | 0.162 | | | | | | |
| SD | 12.05 | 19.58 | 17.08 | 12.50 | | | | | $F(1, 308) = 59.61$ | <0.001 | | $F(1, 308) = 87.81$ | <0.001 | 0.222 | $F(1, 308) = 7.49$ | 0.007 | 0.024 |
| Daily Living Skills | | | | | | | | | | | | | | | | | |
| M | 84.89 | 99.73 | 98.50 | 112.40 | | | | | | | 0.095 | | | | | | |
| SD | 18.09 | 19.61 | 19.61 | 15.97 | | | | | $F(1, 303) = 31.68$ | <0.001 | | $F(1, 303) = 43.97$ | <0.001 | 0.127 | $F(1, 303) < 1.00$ | 0.964 | <0.001 |
| Socialization³ | | | | | | | | | | | | | | | | | |
| M | 77.98 | 97.68 | 93.93 | 109.09 | | | | | | | 0.105 | | | | | | |
| SD | 18.28 | 18.97 | 21.17 | 14.01 | | | | | $F(1, 303) = 35.72$ | <0.001 | | $F(1, 303) = 64.76$ | <0.001 | 0.176 | $F(1, 303) = 1.18$ | 0.279 | 0.004 |

¹Data were missing for Communication (n = 4), Daily Living Skills (n = 9), and Socialization (n = 8) scores

²Age was included as a covariate in the analysis of all three domains

³Race was included as a covariate in the analysis of the Socialization domain