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The Effects of Prenatal Alcohol Exposure and Attention-Deficit/ Hyperactivity Disorder on Psychopathology and Behavior

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Abstract

Background—The present study examined prevalence of psychiatric disorders and behavioral problems in children with and without prenatal alcohol exposure (AE) and attention-deficit/ hyperactivity disorder (ADHD).

Methods—Primary caregivers of 344 children (8–16y, *M*=12.28) completed the Computerized Diagnostic Interview Schedule for Children-IV (C-DISC-4.0) and the Child Behavior Checklist (CBCL). Subjects comprised 4 groups: AE with ADHD (AE+, *n*=85) and without ADHD (AE−, *n*=52), and non-exposed with ADHD (ADHD, *n*=74) and without ADHD (CON, *n*=133). The frequency of specific psychiatric disorders, number of psychiatric disorders (comorbidity), and CBCL behavioral scores were examined using chi-square and ANCOVA techniques.

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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).

Results—Clinical groups had greater frequency of all psychiatric disorders, except for anxiety, where the AE− and CON groups did not differ. There was a synergistic effect of AE and ADHD on conduct disorder. For Comorbidity, children with ADHD had increased psychiatric disorders regardless of AE, which did not have an independent effect on comorbidity. For CBCL scores, there were significant main effects of AE and ADHD on all scores and significant AE X ADHD interactions for Withdrawn/Depressed, Somatic Complaints, Attention, and all Summary scores. There was a synergistic effect of AE and ADHD on Externalizing, Total Problems, and Attention Problems.

Conclusion—Findings indicate that ADHD diagnosis elevates children's risk of psychiatric diagnoses, regardless of AE, but suggest a synergistic relation between AE and ADHD on conduct disorder and externalizing behavioral problems in children. Findings affirm a poorer behavioral prognosis for alcohol-exposed children with ADHD and suggest that more than one neurobehavioral profile may exist for individuals with AE.

Keywords

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

Introduction

The deleterious effects of prenatal alcohol exposure (AE) include a range of neuropsychological and behavioral deficits that fall under the non-diagnostic umbrella term fetal alcohol spectrum disorders (FASD; (Bertrand et al., 2004). Fetal alcohol syndrome (FAS) is on the most extreme end of the spectrum and is diagnosed in the presence of central nervous system (CNS) dysfunction, pre- and post-natal growth deficiencies, and characteristic craniofacial anomalies (i.e., smooth philtrum, thin vermillion border, and small palpebral fissures) (Bertrand et al., 2004; Hoyme et al., 2005; Jones et al., 1973). Although FAS is estimated to occur in 2 to 7 cases per 1,000 live births (May et al., 2009; Sampson et al., 1997), FASDs are more prevalent, and may occur in as many as 2–5% of the population in the U.S. and many Western European countries (May et al., 2009). Children who have histories of AE, with and without the characteristic facial dysmorphology associated with FAS, have impaired intellectual functioning and display similar cognitive and behavioral impairments (Mattson and Riley, 1998; Mattson and Riley, 2000). Cognitive deficits have been documented in neuropsychological domains of executive functioning, learning, memory, language, attention, and social abilities (for review, see (Mattson et al., 2011).

The implications of heavy prenatal exposure to alcohol are long-term and pervasive, affecting the individual's emotional and behavioral functioning throughout the lifespan (Crocker et al., 2009; Fryer et al., 2007; Streissguth et al., 2004). Prognosis is generally poor, with more than half of affected adolescents and adults showing secondary disabilities, including increased psychiatric problems (Fryer et al., 2007; O'Connor and Paley, 2006) and behavioral dysregulation (Disney et al., 2008; Fryer et al., 2007; Mattson and Riley, 2000). In particular, AE has been associated with elevated risk for mood, anxiety, and attachment disorders (D'Onofrio et al., 2007; Fryer et al., 2007; Sayal et al., 2009; Streissguth et al., 2004).

Externalizing behaviors also exist with high frequency in children with AE. Delinquency is highly prevalent in this population, with roughly 35% of adolescents and adults experiencing incarceration and more than half experiencing frequent encounters with law enforcement (Schonfeld et al., 2005; Steinhausen et al., 2003). Furthermore, children with AE often meet diagnostic criteria for disruptive disorders, including oppositional defiant disorder, conduct

disorder, and attention-deficit/hyperactivity disorder (ADHD) (American Psychiatric Association, 2000; Fryer et al., 2007; Steinhausen et al., 2003). Attention difficulties are common, as are increased restlessness and impulsivity (Mattson and Riley, 1998). Interpersonally, children with AE are more self-absorbed than non-exposed peers (Crocker et al., 2009; Steinhausen et al., 2003) and exhibit impaired moral reasoning, communication, and social skills (Carr et al., 2010; Crocker et al., 2009; McGee et al., 2009; McGee and Riley, 2007; Schonfeld et al., 2005). Additional reports of abnormal behavior following AE include inappropriate sexual behaviors, substance abuse, irritability, and sleep problems (Hellemans et al., 2010; Streissguth et al., 2004).

Currently, there are no biological markers of AE in non-dysmorphic children, making clinical diagnosis, and thus accurate identification, difficult (Jones et al., 2006). In addition to the potential lack of dysmorphic features in some children with AE, the high comorbidity of the aforementioned disorders has made it difficult to isolate the teratogenic consequences of AE. In an effort to generate a neurobehavioral profile of AE (e.g., (Mattson et al., 2010b), researchers have begun to compare alcohol-exposed children to other diagnostic groups, specifically non-exposed children with ADHD (for review, see (Mattson et al., 2011). Since 50–80% of individuals with AE are estimated to have ADHD (American Psychiatric Association, 2000; Fryer et al., 2007; Jacobson et al., 2011), the rationale for comparing these two groups includes the need for accurate clinical differentiation and diagnosis (Mattson et al., 2010b). Such comparisons are imperative since the groups may respond differently to stimulant medication (Doig et al., 2008) and behavioral interventions (Peadon et al., 2009).

Prior research has indicated that children with AE and non-exposed children with ADHD exhibit distinct neuropsychological impairments in executive function, verbal and non-verbal memory, and attention domains (Coles et al., 1997; Crocker et al., 2011; Vaurio et al., 2008). However, children with ADHD also exhibit increased levels of psychiatric (Sukhodolsky et al., 2005) and behavioral problems (Murphy and Barkley, 1996; Thorell and Wåhlstedt, 2006). Reports estimate that 60–80% of children and adolescents with ADHD have at least one psychiatric comorbidity (Huh et al., 2011), including mood, anxiety, and conduct disorders (Wilens et al., 2002), which persist into adulthood (Bernardi et al., 2011; Murphy and Barkley, 1996). Additionally, parent and teacher ratings of non-exposed children with ADHD indicate behavioral concerns including increased rates of hostility, aggression, irritability, and delinquency (Huh et al., 2011; Mikami et al., 2007). Parent reports also indicate that children with ADHD have decreased self-control and social functioning (Bernardi et al., 2011; Huh et al., 2011).

Continuing to differentiate children with AE from non-exposed children with ADHD may provide insight as to how secondary disabilities, including psychopathology and maladaptive behavior, arise and impact treatment outcomes. The aim of the current study was to compare prevalence of specific psychiatric disorders and behavioral problems in children with heavy AE with and without ADHD, non-exposed children with ADHD, and controls without histories of AE or ADHD. It was hypothesized that children with AE, regardless of ADHD diagnosis, and non-exposed children with ADHD would have elevated rates of psychiatric disorders. The current study also sought to examine whether behavioral problems following AE were affected by the presence of ADHD. We expected that children with both AE and ADHD would exhibit greater rates of behavioral problems compared to controls or children with either AE or ADHD alone.

Methods

General Methods

Children (*N*=344) between the ages of 8–16 (*M*=12.28, *SD*=2.46) years were recruited for an ongoing multisite study conducted by the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD; (Mattson et al., 2010a). The CIFASD clinical projects have been described previously (Mattson et al., 2010a). For this study, which was a part of the second data collection phase (CIFASD II), data from children with and without AE and with and without a diagnosis of ADHD were analyzed.

Children with AE were recruited retrospectively and had confirmed histories of heavy prenatal alcohol exposure, defined as prenatal exposure to more than four alcoholic drinks at least once per week or at least 13 drinks per week throughout the pregnancy. Confirmation of AE occurred through several modalities including, medical history, birth records, social services records, and, when available, maternal report. Each child underwent a standardized assessment of physical, craniofacial and growth anomalies by a member of the CIFASD Dysmorphology Core to determine FAS diagnosis. Children with AE were diagnosed as having FAS if they met the following CIFASD Dysmorphology Core diagnostic criteria: structural abnormality (two or more of the following facial features: short palpebral fissure length, smooth philtrum, thin vermillion border) and either growth deficiency or microcephaly (for more details, see (Jones et al., 2006).

Testing took place at multiple testing centers across the United States and recruitment methods differed by site location. Subjects were recruited for this study from the following 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 different 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. All groups were recruited from all sites as part of ongoing research initiatives or specifically for the CIFASD study (Mattson et al., 2010a).

Comparison subjects were screened for AE and were only included if AE levels were less than minimal exposure, defined as no more than one drink per week on average and never more than two drinks on a single occasion throughout gestation. General exclusion criteria for all groups were if the child was a non-fluent English speaker, had history of significant head injury or loss of consciousness greater than 30 minutes, had been adopted from abroad after the age of 5 years old or less than 2 years before assessment, or had a psychiatric or physical disability that prevented successful study completion (e.g., active psychosis or autism).

Each child was administered a standardized neuropsychological battery in a single day by a trained examiner, who was blind to subject group. Different domains of functioning were assessed, including general intellectual functioning, attention, memory, and executive functioning. Parent interviews and questionnaires were administered to primary caregivers. Caregivers completed the clinician-assisted National Institute of Mental Health Diagnostic Interview Schedule for Children IV (C-DISC-4.0; (Shaffer et al., 2000) and the Child Behavior Checklist (CBCL; Achenbach, 1991), among other behavioral reports. Informed consent and assent were obtained from all subjects and their legal guardians prior to testing. Subject incentive was provided to both parents and children. The Institutional Review Board (IRB) at San Diego State University and other CIFASD sites approved this study.

Subjects

Children with AE were divided into two groups: those meeting *DSM-IV* criteria for ADHD per the C-DISC-4.0 (AE+; *n*=85) and those who did not meet criteria for ADHD (AE−; *n*=52). Of the children with AE, 38 (27.7%) met diagnostic criteria for FAS (AE+ n=15, AE − n=23). The ADHD group (*n*=74) consisted of non-exposed children who met *DSM-IV* diagnostic criteria for ADHD per the C-DISC-4.0. The CON group (*n*=133) consisted of children who did not have AE or meet diagnostic criteria for ADHD. Children were excluded from the CON group if they demonstrated subclinical symptoms of ADHD, as defined by the C-DISC-4.0 (Shaffer et al., 2000).

Measures

Computerized Diagnostic Interview Schedule for Children Version IV (C-DISC)—The C-DISC-4.0 is a computerized clinician-assisted structured diagnostic instrument that assesses clinical symptoms experienced by the child during the past *year*, *month*, and *whole life* (American Psychiatric Association, 2000; Shaffer et al., 2000). Only positive diagnoses during the last year were assessed in the current analysis. The C-DISC-4.0 covers mood and developmental disorders as defined by the *DSM-IV* and diagnosis is provided through algorithms derived from the computer software package. A comprehensive evaluation of psychopathology was not undertaken in this study in order to limit the time requirements and subject burden of this large, multidimensional study (Mattson et al., 2010a). Instead, the following disorders were examined: Generalized Anxiety Disorder (GAD), Major Depressive Disorder (MDD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD). These disorders are known to be elevated in both AE and ADHD (Huh et al., 2011).

Child Behavior Checklist (CBCL)—The CBCL is a parent-completed survey assessing behavior in children between the ages of 6–18 years. The CBCL is completed in a single 15–20 minute session. Parents/caregivers are instructed to answer questions about their child's behavior during the past 6 months. Items are scored as follows: 0=*Not True (as far as you know)*, 1=*Somewhat or Sometimes True*, or 2=*Very True or Often True*. For the purposes of this study, items from the Problem scales (Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, Aggressive Behavior) and Summary (Internalizing Problems, Externalizing Problems, and Total Problems) scores were examined. Scoring of the CBCL is completed through a computer-based program that generates raw and normalized *T*-scores for the CBCL Problem scale and Summary scores. Higher raw and *T*-scores are indicative of more severe and frequent behavioral problems.

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, handedness and home placement] and standard analysis of variance (ANOVA) [age and FSIQ]. Significant group differences on ANCOVA were further examined using pair-wise comparisons [Tukey's Honestly Significant Difference (HSD) test].

Chi-square tests of independence analyses were used to determine whether groups differed on prevalence of specific *DSM-IV* diagnoses (GAD, MDD, ODD, and CD). Significant omnibus tests were followed up with pairwise Chi-square comparisons. In addition, to examine group differences on rates of overall number of psychiatric diagnoses, a Comorbidity variable was created by summing the number of positive diagnoses for GAD, MDD, ODD, and CD for each participant. A Comorbidity score of 0 indicated no diagnoses and a score of 4 indicated the presence of all 4 disorders. The Comorbidity variable was analyzed using a 2 (AE: positive, negative) X 2 (ADHD diagnosis: positive, negative)

analysis of covariance (ANCOVA). Race, ethnicity, home placement, and sex were included as covariates. An alpha per test rate of .05 was used to test the effects of AE, ADHD, and their interaction on Comorbidity.

The CBCL Problem scales and CBCL Summary (Internalizing, Externalizing, and Total Problems) scores were analyzed with two, 2 (AE) X 2 (ADHD diagnosis) between-subjects multivariate analysis of covariance (MANCOVA) tests. Race, ethnicity, home placement, and sex were included as covariates. Significant results were followed up with univariate analyses and pairwise comparisons. An alpha per test rate of .05 was used for all omnibus effects, and a more stringent alpha per test rate of .01 was used to determine significance of all follow-up tests.

Results

Demographic Data

Groups differed on race [χ^2 (df=3)=12.61, p=.006], ethnicity [χ^2 (df=3)=9.29, p=.026], sex [χ^2 (df=3)=13.78, p=.003], home placement [χ^2 (df=3)=122.59, p<.001] and Full Scale IQ [FSIQ; F(3, 343)=72.86, p<.001] but not on handedness [χ^2 (df=3)=2.88, p=.410] or age [F(3, 343)=1.49, p=. 218]. Demographic information and pairwise comparisons are presented in Table 1.

Analysis of C-DISC-4.0 Psychiatric Measures

Frequency of individual psychiatric diagnoses—Omnibus tests indicated that groups differed significantly on frequency of GAD, MDD, ODD, and CD. With one exception (GAD), all three clinical groups had higher frequencies than the CON group. Synergistic effects were present for CD, whereby children with both AE and ADHD had a higher frequency of CD than children in the AE− and ADHD groups, which did not differ from each other. The frequency of GAD, MDD, ODD, and CD for each group and statistical results are shown in Table 2.

Number of psychiatric diagnoses (comorbidity)—The ANCOVA results (see Table 3) revealed a significant main effect of ADHD diagnosis, indicating that children with ADHD had significantly more diagnoses than children without ADHD, regardless of AE. Neither the main effect of AE nor the AE X ADHD diagnosis interaction were significant. Thus, after controlling for ADHD diagnosis, AE was not independently associated with elevated rates of the psychiatric disorders examined herein. None of the covariates were significantly associated with Comorbidity (p>.05).

Analysis of CBCL Behavioral Data

Problem scales—Due to violations of homogeneity of variance-covariance assumptions, Wilks' Lambda criterion was used as the omnibus test statistic. MANCOVA results revealed significant main effects for AE [F(8, 297)=5.982, p<.001] and ADHD diagnosis [F(8, 297)=39.633, p<.001], and a significant AE X ADHD diagnosis interaction [F(8, 297)=3.712, p<.001] on Problem scales. Of the covariates, only race was significant [F(8, 297)=2.262, p=.023]. None of the other covariates were significantly associated with Problem scales (p>.05).

To probe the statistically significant multivariate effects, 2 × 2 ANCOVAs were conducted on each Problem scale (see Table 4). There were statistically significant main effects for AE and ADHD diagnosis on all Problem scales (p<.003). Children with histories of AE had higher problem behavior scores than children without AE, regardless of ADHD diagnosis and children with ADHD had higher problem behavior scores than children without ADHD,

regardless of AE. The AE X ADHD diagnosis interaction effects were statistically significant for Withdrawn/Depressed, Somatic Complaints, and Attention Problems scales. Follow-up pairwise comparisons indicated that for these three problem scales, the three clinical groups had higher scores than the control group but only differed from each other on Attention Problems. Further, there was a synergistic effect of AE and ADHD on the Attention Problems scale whereby children with AE and ADHD had higher scores than children with either condition alone.

Summary scores—Due to violations of homogeneity of variance-covariance assumptions, Wilks' Lambda criterion was used as the omnibus test statistic. The MANOVA revealed significant main effects for AE [$F(3, 302)=16.136$, $p<.001$] and ADHD [$F(3, 302)=85.367$, $p<.001$] diagnosis, and a significant AE X ADHD diagnosis interaction [$F(3, 302)=6.606$, $p<.001$]. None of the covariates were significantly associated with Summary scores ($p>.05$). To probe the statistically significant multivariate effects, univariate 2 × 2 ANCOVAs were conducted on each Summary score (see Table 4). There were statistically significant main effects for AE and ADHD diagnosis on all three CBCL Summary scores ($p<.001$). Thus, children with histories of AE had significantly higher scores than children without AE, regardless of ADHD diagnosis and children with ADHD had significantly higher scores than children without ADHD, regardless of AE. The AE X ADHD diagnosis interaction was also statistically significant for all CBCL Summary scores ($p<.002$). Follow-up pairwise comparisons indicated that for all summary scores, the three clinical groups had higher scores than the control group. Further, there was a synergistic effect of AE and ADHD on the Externalizing and Total summary scores, whereby children with AE and ADHD had higher scores than children with either condition alone.

Impact of FAS diagnosis on Comorbidity and Behavior

Results were repeated within the AE group to determine if the presence of an FAS diagnosis affected the findings. Alcohol-exposed children with and without FAS had similar rates of GAD, MDD, ODD, and CD ($p>.192$). Additionally, results of these analyses indicated that an ADHD, but not FAS diagnosis was associated with higher frequency of disorders and greater behavioral problems. Details of the behavioral findings can be found in supplemental tables.

Discussion

The current study assessed group differences on frequency of four specific psychiatric disorders, the comorbidity of these disorders, and behavioral problems in children with histories of AE with and without ADHD, non-exposed children with ADHD, and controls without AE or ADHD. We hypothesized that children in the AE+, AE−, and ADHD groups would have elevated rates of specific diagnoses, higher comorbidity rates, and more severe parent-rated behavioral problems compared to children in the CON group.

In part, the current findings supported our initial hypotheses. In terms of the frequency of specific disorders, the clinical groups exhibited significantly higher rates of GAD, MDD, ODD, and CD than controls, with the exception of GAD where the AE− and CON groups did not differ. However, children in the AE+ had higher rates than the AE− group on the frequency of disruptive disorders (ODD and CD), but had similar rates of GAD and MDD. Contrary to what was expected, there were some differences between the ADHD and AE− groups, with the ADHD group exhibiting higher rates of GAD and ODD but not CD or MDD. Finally, the ADHD groups (AE+, ADHD) were similar on rates of GAD, MDD, and ODD. However, there appears to be a combined effect of AE and ADHD on the frequency

of CD wherein the combination of these two effects (the AE+ group) was greater than either effect alone.

Comorbidity was also higher in all three clinical groups than in the CON group, as expected, and both groups with ADHD (the AE+ and ADHD groups) had greater comorbidity than subjects without ADHD. However, the main and interactive effects involving AE were not significant suggesting that the presence of ADHD is a risk factor for other psychiatric disorders but that AE is not independently related to comorbidity. Within the AE group, the presence of an FAS diagnosis did not change these results. Thus, findings indicate that the presence of ADHD, but not FAS or AE alone, is related to a greater number of psychiatric disorders.

Findings from the parent-reported behavioral measures suggest that both AE and ADHD are important in the prediction of maladaptive behavior. Children with AE (the AE+ and AE− groups) had higher scores than children without AE (the ADHD and CON groups) and children with ADHD (the AE+ and ADHD groups) had higher scores than the children without ADHD (the AE− and CON groups). However, significant AE X ADHD interactions suggested a synergistic effect of AE and ADHD for Attention, Externalizing, and Total Problems scales. On these measures, the AE+ group had higher scores than the AE−, ADHD and CON groups. Thus, AE and ADHD alone result in attention, externalizing, and overall behavioral deficits, but having AE and ADHD worsens problems beyond what would be expected from AE or ADHD alone. These results support another recent CIFASD study showing that specific aspects of ADHD are similar in children with ADHD with and without AE (Graham et al., 2011). In addition, results were similar when repeated within the AE group; the presence of an FAS diagnosis did not influence behavioral outcome. Such findings support prior research of neurobehavioral similarities in alcohol-exposed children with and without FAS (e.g., Mattson and Riley, 1998; Mattson and Riley, 2000). In contrast, these results do suggest that for children with AE, a diagnosis of ADHD, but not FAS, is associated with greater behavioral problems

The current study adds to the growing literature on AE that seeks to identify and differentiate children who do and do not have histories of heavy AE. Current findings support previous studies suggesting that children with AE and non-exposed children with ADHD are at greater risk for psychiatric and behavioral problems than non-exposed children (for review, see Mattson et al., 2011). Specifically, these results emphasize previously supported associations between AE and aggressive, delinquent, and disruptive behavioral problems (D'Onofrio et al., 2007; Mattson and Riley, 2000; Schonfeld et al., 2005), and extends findings by demonstrating that problems may be associated with the presence of ADHD, as the AE+ group exhibited the greatest number of disruptive disorders. These results are not surprising given current and previous findings of elevated rates of disruptive disorders, including ODD and CD, in non-exposed children with ADHD (Bernardi et al., 2011).

Several recent studies have examined neuropsychological differences between alcohol-exposed children and non-exposed children with ADHD and suggest that the effects of AE and ADHD can be distinguished from each other on some neuropsychological domains, including attention, executive functioning, and numerical processing (for review, see Mattson et al., 2011). This is the first study to compare the effects of AE and ADHD on psychiatric measures. Findings suggest similarities between AE and ADHD on these outcomes; both AE and ADHD have independent negative effects on behavioral and psychiatric impairments in children. However, the current study suggests that while the effect of ADHD is greater than the effect of AE on comorbidity overall, there is a synergistic relationship between AE and ADHD that worsens psychiatric and behavioral outcomes.

Specifically, the combination of AE and ADHD was worse than either effect alone on the presence of CD and the severity of attention and externalizing behavior problems in this sample. These results imply that more than one behavioral phenotype may exist in AE. Specifically, the different psychiatric and behavioral outcomes for alcohol-exposed children with ADHD compared to those without ADHD demonstrate that the risk of secondary deficits may be greater in the presence of AE and ADHD. Such differences in psychiatric and behavioral outcomes suggest that children with both AE and ADHD may require more specialized and tailored interventions and treatments.

Limitations

Despite the novel findings of this study, there are several limitations to be considered. Though variables related to childhood mental health outcomes, including race, ethnicity, and home placement were covaried in the current analysis socioeconomic status (SES) was not. Since the current investigation is part of an ongoing international study a measures of SES was not available for the participants in the current study. Low SES has been linked with adverse mental health outcomes including risk for psychiatric and behavioral problems in children (Bastiaansen et al., 2005), and is associated with ADHD severity (Pressman et al., 2006). Therefore, future research needs to further investigate the role of SES on psychiatric and behavioral outcomes in AE. Similarly, IQ was not included as a covariate in these analyses given that low IQ is inherent in the effects of prenatal alcohol exposure and the arguments against covarying IQ in neurodevelopmental disorders (Dennis et al., 2009). Additionally, the current study examined a broad age range, and results may not apply to more specific ages. Age could also impact behavioral assessments, as behavioral requirements and functioning may not be as restrictive in younger children with AE or ADHD as for older children.

Furthermore, since the current study assessed a large cohort of children using multidimensional assessment, we only investigated a limited number of psychiatric diagnoses that have been previously documented in children with AE. However, prior research has indicated high rates of other psychiatric disorders, including attachment disorder, specific depressive disorders, and specific phobias in children with AE (D'Onofrio et al., 2007; Fryer et al., 2007; Sayal et al., 2009; Streissguth et al., 2004). Thus, these results should be followed up with a more extensive investigation of psychiatric comorbidity in children who have AE and ADHD. For example, further investigation of comorbid diagnoses associated with both AE and ADHD, including obsessive-compulsive and tic disorder, would be clinically beneficial and may help to understand the clinical disparities between these groups.

Strengths

The current investigation has several notable strengths. This is the first study to differentiate between children who have AE with and without ADHD on psychiatric measures. Though there are several studies examining parent-rated behavior in children with AE (e.g., Mattson and Riley, 2000), this is the first to address whether the relationship between AE and behavior is affected by ADHD by separating the AE group into those with and without this diagnosis. Other strengths include the notable sample size. This study examined a large group of children considered to have histories of heavy AE. Further, 30% of the alcohol-exposed children had FAS and the average IQ scores of AE+ and AE− groups were 81 and 87, respectively, suggesting that this AE sample is representative of the population of children with heavy AE. Additionally, 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.

Summary and Future directions

As a whole, these results indicate that the presence of both AE and ADHD lead to psychiatric and behavioral symptoms, which are greater in severity and distinguishable from those seen in AE without ADHD. Results suggest that both AE and ADHD result in behavioral impairments, and that behavioral deficits are worsened in the presence of both AE and ADHD, particularly for externalizing disorders (e.g., CD and attention problems). In order to distinguish between the effects of AE and ADHD, future research should examine whether or not children with AE with and without ADHD differ on neuropsychological domains, such as attention, executive function, learning, and memory. A possible alternative to the analysis strategy used in this paper is to test whether ADHD moderates the association between prenatal alcohol exposure and psychiatric/behavioral outcomes. Disentangling teratogenic effects of AE from those associated with ADHD may help to clarify whether AE causes ADHD directly, or, more likely, that AE causes deficits in critical aspects of cognition and behavior that then cause a child to meet criteria for ADHD. The latter hypothesis is consistent with the idea that ADHD is best explained by multiple neurodevelopmental pathways (Sonuga-Barke, 2005). Also, continuing to examine the direct effects of heavy AE, with and without the presence of ADHD, will allow researchers and clinicians to create effective interventions for children with AE. Since such a high percentage of children with AE exhibit ADHD symptoms, future research needs to consider how comorbid ADHD diagnosis affects treatment outcomes and prognosis.

Additionally, these findings should be utilized in guiding interventions and treatments for children with histories of AE. Since psychiatric comorbidity and behavioral problems following AE are exacerbated in the presence of ADHD, future research should consider psychiatric comorbidity as a possible mediator on treatment outcome. Similarly, these results demonstrate that children with AE with and without ADHD need to be further differentiated by clinicians and researchers, as these findings suggest they may have different behavioral outcomes and clinical presentations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic data for children with prenatal alcohol exposure with ADHD (AE+), with prenatal alcohol exposure without ADHD (AE−), non-exposed children with ADHD (ADHD), and controls (CON).

Demographic Variable	AE+ (n=85)	AE− (n=52)	ADHD (n=74)	CON (n=133)	Pairwise
CIFASD Site [N (%)]					
Atlanta	15 (17.6)	12 (23.1)	16 (21.3)	19 (14.6)	
Los Angeles	16 (18.8)	10 (19.2)	2 (2.7)	18 (13.8)	
Northern Plains	13 (15.3)	8 (15.4)	8 (10.8)	16 (12.0)	
New Mexico	7 (8.2)	5 (9.6)	11 (14.7)	20 (15.4)	
San Diego	34 (40.1)	17 (32.7)	37 (49.3)	60 (43.1)	
Handedness [N (%Right)]	73 (85.9)	48 (92.3)	67 (90.7)	123 (92.5)	
FAS [N (%)]	23 (27.1)	15 (28.8)	0 (0)	0 (0)	AE+ = AE−
Home Placement [N (% Biological)]*	26 (30.6)	27 (51.9)	61 (82.4)	128 (96.2)	AE+ > AE− > ADHD > CON
Sex [N (% Males)]*	51 (61.3)	24 (20.5)	56 (73.6)	71 (53.4)	AE+, AE−, CON < ADHD
Race [N (%White)]*	55 (64.7)	25 (48.1)	55 (74.3)	105 (78.9)	AE− < AE+, ADHD, CON
Ethnicity [N (%Hispanic)]*	7 (8.2)	12 (28.2)	19 (23.6)	27 (18.5)	AE+ < AE−, ADHD, CON
Age [M (SD)]	12.42 (2.39)	12.44 (2.38)	11.70 (2.46)	12.44 (2.53)	
FSIQ [M (SD)]*	81.64 (17.10)	87.35 (14.93)	92.16 (18.53)	110.49 (11.79)	AE+ < AE−, ADHD < CON

* $p<.05$

Table 2

Rates [n (%)] of Generalized Anxiety Disorder (GAD), Major Depressive Disorder (MDD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD) for children with prenatal alcohol exposure with ADHD (AE+) and without ADHD (AE−), non-exposed children with attention-deficit/ hyperactivity disorder (ADHD), and controls (CON).

Diagnosis	AE+ (n=85)	AE− (n=52)	ADHD (n=74)	CON (n=133)	χ^2 (*df*=1)	*p*-value	Pairwise Comparisons (*p*)
GAD	5 (5.9)	1 (1.9)	9 (12.2)	0 (0)	18.08	<0.001	AE+ = AE− (.272) AE+ = ADHD (.163) AE+ > CON (0.005) ADHD > AE− (.036) ADHD > CON (<.001) AE− = CON (.109)
MDD	6 (7.1)	3 (5.8)	12 (16.2)	0 (0)	21.99	<.001	ADHD = AE+ (.075) ADHD = AE− (.069) AE+ = AE− (.767) AE+, AE−, ADHD > CON (<.005)
ODD	41 (48.2)	6 (11.5)	34 (45.9)	5 (3.8)	78.82	<.001	AE+ > AE− (<.001) AE+ > CON (<.001) AE+ = ADHD (.773) ADHD > AE− (<.001) ADHD > CON (<.001) AE− > CON (.044)
CD	16 (18.8)	2 (3.8)	4 (5.4)	0 (0)	31.70	<.001	AE+ > AE− (.012) AE+ > ADHD (.010) AE+ > CON (<.001) ADHD > CON (<.001) AE− = ADHD (.686) AE− > CON (<.023)

Table 3

Rates [n (%)] of comorbid Generalized Anxiety Disorder (GAD), Major Depressive Disorder (MDD), Oppositional Defiant Disorder (ODD), Conduct Disorder (CD) diagnoses and ADHD X AE ANCOVA (controlling for home placement, ethnicity, sex, and race) results for children with prenatal alcohol exposure with ADHD (AE+) and without ADHD (AE−), non-exposed children with attention-deficit/hyperactivity disorder (ADHD), and controls (CON).

	Exposed		Unexposed		ADHD Main Effect		AE Main Effect		ADHD X AE Interaction	
Number of Positive Diagnoses *	**AE+ (n=85)**	**AE− (n=52)**	**ADHD (n=74)**	**CON (n=133)**	***F (1, 340)***	***p***	***F (1, 340)***	***p***	***F (1, 340)***	***p***
0	40 (47.1)	43 (82.7)	38 (51.4)	128 (96.2)	67.26	*<.001*	1.46	.228	1.38	.241
1	28 (32.9)	6 (11.5)	21 (28.4)	5 (3.8)						
2	12 (14.1)	3 (5.8)	9 (12.2)	0 (0)						
3	4 (4.7)	0 (0)	4 (5.4)	0 (0)						
4	1 (1.2)	0 (0)	2 (2.7)	0 (0)						
Mean (SD)	.80 (.94)	.23 (.55)	.80 (1.03)	.04 (.19)						

*excludes ADHD diagnoses.

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Table 4

CBCL MANCOVA results for children with prenatal alcohol exposure with ADHD (AE+) and without ADHD (AE−), non-exposed children with attention-deficit/hyperactivity disorder (ADHD), and controls (CON) while controlling for home placement, ethnicity, sex, and race.

	Exposed		Unexposed		ADHD Main Effect		AE Main Effect		ADHD X AE Interaction		Pairwise Comparisons*
	AE+ (n=85)	AE− (n=52)	ADHD (n=74)	CON (n=133)	*F* (1, 304)	*p*	*F* (1, 304)	*p*	*F* (1, 304)	*p*	
Problem Scales											
Anxious/Depressed											
M	61.55	55.86	60.26	52.17	53.94	<.001	9.70	.002	1.81	.180	
SD	8.95	7.11	10.07	4.28							
Withdrawn/Depressed											
M	58.24	57.02	59.08	52.36	18.88	<.001	9.25	.003	11.32	.001	AE+, AE−, ADHD > CON
SD	7.09	7.52	8.53	3.86							
Somatic Complaints											
M	60.64	59.51	59.36	53.45	15.31	<.001	16.95	<.001	7.12	.008	AE+, AE−, ADHD > CON
SD	9.08	9.10	8.80	5.36							
Social Problems											
M	66.11	57.35	61.01	51.80	106.87	<.001	24.86	<.001	<1	.942	
SD	9.16	7.41	8.63	3.63							
Thought Problems											
M	66.96	57.55	62.64	52.33	116.19	<.001	16.85	<.001	<1	.871	
SD	8.70	8.45	9.02	3.76							
Attention Problems											
M	73.09	59.96	68.56	51.33	304.16	<.001	39.36	<.001	6.00	.015	AE+ > ADHD > AE− > CON
SD	9.44	8.50	8.47	2.68							
Rule-Breaking Behavior											
M	64.09	58.06	60.24	52.06	61.33	<.001	17.16	<.001	<1	.371	
SD	8.41	7.12	8.30	3.98							

	Exposed		Unexposed		ADHD Main Effect		AE Main Effect		ADHD X AE Interaction		Pairwise Comparisons*
	AE+ (n=85)	AE− (n=52)	ADHD (n=74)	CON (n=133)	*F* (1, 304)	*p*	*F* (1, 304)	*p*	*F* (1, 304)	*p*	
Aggressive Behavior											
M	67.54	57.49	61.10	51.60	85.86	<.001	26.33	<.001	<1	.803	
SD	11.37	8.27	9.51	3.23							
Summary Scores											
Internalizing Summary											
M	60.73	55.47	58.88	45.52	50.48	<.001	22.32	<.001	9.98	.002	AE+ > AE− > CON AE+, ADHD > CON AE−, ADHD > CON
SD	10.15	10.65	11.44	9.39							
Externalizing Summary											
M	65.76	56.02	59.78	43.05	106.97	<.001	37.23	<.001	8.56	.004	AE+ > AE−, ADHD > CON
SD	9.84	9.81	10.55	9.10							
Total Summary											
M	68.01	56.59	63.33	41.72	184.87	<.001	46.61	<.001	17.71	<.001	AE+ > ADHD > AE− > CON
SD	8.03	10.56	8.59	10.24							

*Pairwise comparisons only provided for significant interaction effects. Alpha levels for pairwise comparisons were set at $p < .01$.