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Leila Glass, *San Diego State University*
Ashley L. Ware, *San Diego State University*
Nicole Crocker, *San Diego State University*
Benjamin N. Deweese, *San Diego State University*
Claire Coles, *Emory University*
Julie Kable, *Emory University*
Philip A. May, *University of North Carolina*
Wendy O. Kalberg, *University of New Mexico*
Elizabeth R. Sowell, *University of New Mexico*
Kenneth Lyons Jones, *University of California San Diego*

Only first 10 authors above; see publication for full author list.

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NEUROPSYCHOLOGICAL DEFICITS ASSOCIATED WITH HEAVY PRENATAL ALCOHOL EXPOSURE ARE NOT EXACERBATED BY COMORBID ADHD

Leila Glass[1], **Ashley L. Ware**[1], **Nicole Crocker**[1], **Benjamin N. Deweese**[1], **Claire D. Coles**[2,3], **Julie A. Kable**[3], **Philip A. May**[4,5], **Wendy O. Kalberg**[5], **Elizabeth R. Sowell**[6,7], **Kenneth Lyons Jones**[8], **Edward P. Riley**[1], **Sarah N. Mattson**[1], and **CIFASD**[*]

[1] Center for Behavioral Teratology, Department of Psychology, San Diego State University, San Diego, CA 92120

[2] Department of Psychiatry and Behavior Sciences, Emory University School of Medicine, Atlanta, GA 30322

[3] Department of Pediatrics, Emory University School of Medicine, Atlanta, GA 30322

[4] Department of Nutrition, Gillings School of Global Public Health, University of North Carolina Nutrition Research Institute, Kannapolis, NC 28081

[5] Center on Alcoholism, Substance Abuse and Addictions, The University of New Mexico, Albuquerque, NM 87131

[6] Developmental Cognitive Neuroimaging Laboratory, Department of Pediatrics, Keck School of Medicine, University of Southern California.

[7] Division of Research on Children, Youth, and Families, Department of Pediatrics, Children's Hospital Los Angeles, LA CA 90027.

[8] University of California, San Diego, School of Medicine, Department of Pediatrics, San Diego, CA 92093

Abstract

Objective: Neuropsychological functioning of individuals with attention-deficit/hyperactivity disorder (ADHD) or heavy prenatal alcohol exposure has been well documented independently. This study examined the interaction between both factors on cognitive performance in children.

Method: As part of a multisite study, 344 children (8-16y, *M*=12.28, *SD*=2.52) completed a comprehensive neuropsychological battery. Four subject groups were tested: children with histories of heavy prenatal alcohol exposure (AE) and ADHD (AE+, *n*=90), alcohol-exposed without ADHD, (AE−, *n*=38), non-exposed with ADHD (ADHD, *n*=80), and non-exposed without ADHD (CON, *n*=136).

Results: Separate 2(AE) × 2(ADHD) MANCOVAs revealed significant main and interactive effects of ADHD and AE on overall WISC-IV, D-KEFS, and CANTAB performance. Individual ANOVAs revealed significant interactions on 2 WISC-IV indices [Verbal Comprehension (VCI), Perceptual Reasoning (PRI)], and four D-KEFS and CANTAB subtests [Design Fluency, Verbal Fluency, Trail Making, Spatial Working Memory]. Follow-up analyses demonstrated no difference between AE+ and AE− groups on any measures. The combined AE+/− group demonstrated more severe impairment than the ADHD group on VCI and PRI, but there were no other differences between clinical groups.

Conclusions: These results support a combined AE+/− group for neuropsychological research and indicate that, in some cases, the neuropsychological effects seen in ADHD are altered by prenatal alcohol exposure. The effects of alcohol exposure on verbal comprehension and perceptual reasoning were greater than those related to having ADHD without alcohol exposure, although both conditions independently resulted in cognitive impairment compared to controls. Clinically, these findings demonstrate task-dependent patterns of impairment across clinical disorders.

Keywords

Heavy prenatal alcohol exposure is a leading cause of birth defects, developmental disorders, and intellectual disability (American Academy of Pediatrics Committee on Substance Abuse and Committee on Children With Disabilities, 2000). Attention-deficit/hyperactivity disorder (ADHD) is also a significant contributor to developmental disability and the most common childhood behavioral issue (Blanchard, Gurka, & Blackman, 2006; Williams, Klinepeter, Palmes, Pulley, & Foy, 2004). Children with histories of heavy prenatal alcohol exposure or ADHD are at risk for a wide range of impairments including behavioral and neuropsychological deficits. Although alcohol-exposed children often meet diagnostic criteria for ADHD (Fryer, McGee, Matt, Riley, & Mattson, 2007), the interaction between these clinical disorders on neuropsychological function is unclear.

The devastating neuropsychological, behavioral and physical effects of heavy prenatal alcohol exposure occur on a continuum. Fetal alcohol spectrum disorders (FASD) encompass the wide range of outcomes resulting from heavy prenatal alcohol exposure, including neuropsychological and neurobehavioral deficits, and pertains to affected children with and without fetal alcohol syndrome (FAS; Mattson & Riley, 1998; Mattson, Riley, Gramling, Delis, & Jones, 1997, 1998). While the presence of FAS (Bertrand, Floyd & Weber, 2005; Hoyme et al., 2005) enables identification of some children with histories of heavy prenatal alcohol exposure, most affected individuals do not exhibit obvious dysmorphology, which greatly hinders identification (Bertrand, et al., 2005; Sampson et al., 1997). Children with heavy prenatal alcohol exposure who do not meet the specific diagnostic criteria for FAS may still exhibit similar neuropsychological impairments as those with FAS and thus, current research generally combines heavily exposed individuals with and without FAS in order to study the full range of deficits resulting from alcohol's effects (e.g., Mattson, Crocker, & Nguyen, 2011; Mattson & Riley, 1998; Mattson, Riley, Gramling, Delis, & Jones, 1997, 1998). Current estimated prevalence rates are 0.2-0.7% for

FAS, and 2-5% for FASD (May et al., 2009). Higher rates of FAS and FASD have been documented internationally (May et al., 2000).

Variability in degrees of impairment, and the lack of fully encompassing diagnostic physical features complicate accurate clinical identification of alcohol-exposed children (Mattson & Riley, 2011). In an attempt to improve identification of non-dysmorphic alcohol-exposed children across the spectrum of effects, research has increasingly focused on the development of a differential profile of neuropsychological and behavioral abilities in children with FASD. If successful, the profile would facilitate more precise diagnostic criteria for identification and improve treatment by specifically defining the nature of alcohol-related deficits (Mattson & Riley, 2011). Neuropsychological impairments of children with heavy prenatal alcohol exposure occur across a wide range of cognitive domains (for review see Mattson, Crocker, et al., 2011). These impairments can be devastating and lifelong, (for review, see Bay & Kesmodel, 2011; Coles, Lynch, Kable, Johnson, & Goldstein, 2010; Kable & Coles, 2004; Mattson & Riley, 1998). Even with continued effort to refine the neurobehavioral profile of FASD, neither the range of deficits nor their specificity, is fully understood.

The overlap with other distinct clinical conditions with similar clinical presentations, such as ADHD, further limits the ability to specifically identify alcohol-exposed individuals, especially those without FAS (Mattson & Riley, 2011). Rates of ADHD in FASD are much higher than the rates in the general population (for review see O'Connor & Paley, 2009), and exceed 60% in the U.S. (Fryer, et al., 2007) and Canada (Rasmussen et al., 2010), including Native American populations (Burd, Klug, Martsolf, & Kerbeshian, 2003), and Eastern European adoptees (Landgren, Svensson, Strömland, & Grönlund, 2010). Children with a diagnosis of ADHD present with neuropsychological impairments similar to those apparent in alcohol-exposed children (e.g., executive functioning deficits and attention impairment (for review see Mattson, Crocker, et al., 2011), which further hinders differentiation between the disorders. Subsequently, a critical area of research has emerged, focusing on differentiation of neurobehavioral impairments in alcohol-exposed children from impairments that are typical of non-exposed children with ADHD (Coles et al., 1997; Crocker, Vaurio, Riley, & Mattson, 2009; Crocker, Vaurio, Riley, & Mattson, 2011; Greenbaum, Stevens, Nash, Koren, & Rovet, 2009; Kooistra, Crawford, Gibbard, Ramage, & Kaplan, 2010; Kooistra et al., 2009; Vaurio, et al., 2008). Studies have also compared children with ADHD with and without prenatal alcohol exposure (Burden et al., 2010). A small number of studies have been recently conducted comparing alcohol-exposed children with and without concomitant ADHD focused on behavioral functioning, including sluggish cognitive tempo, adaptive behavior, psychopathology, and problem behaviors (Graham et al., 2012; Ware, Crocker, et al., 2012; Ware, O'Brien, et al., 2012). These behavioral studies found exacerbated effects of having both prenatal alcohol exposure and ADHD compared to alcohol exposure alone. In contrast, neuropsychological function has not been adequately examined with this design. Although one small study found minimal differences between alcohol-exposed children with and without ADHD on measures of attention, cognition, communication, memory, executive function and adaptive behavior (Rasmussen, et al., 2010), there was no control group against which to gauge performance of the alcohol-exposed subjects. Given these results, research addressing the combined effect of alcohol exposure and ADHD on neuropsychological abilities is necessary to understand possible exacerbated effects, facilitate identification, and inform therapeutic interventions.

This study aimed to extend current knowledge on understanding the effects of heavy prenatal alcohol exposure and ADHD, both in conjunction and independently, on three major assessment measures of neuropsychological functioning. Based on the previous behavioral studies showing exacerbated deficits in children with prenatal alcohol exposure

and ADHD, beyond the impairment expected for each disorder individually, we hypothesized that (1) children in the clinical groups (e.g., those with either heavy prenatal alcohol exposure or an ADHD diagnosis or both), would show deficits in neuropsychological functioning compared to controls, and (2) alcohol-exposed children with ADHD would exhibit more severe neuropsychological impairments compared to alcohol-exposed children without ADHD or non-exposed children with ADHD.

Method

Subjects

Children ($N = 344$) between the ages of 8-16 years ($M = 12.28$, $SD = 2.52$) were recruited for an ongoing multisite study conducted by the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). The clinical projects included in the CIFASD have been described previously (Mattson et al., 2010). Recruitment methods differed by site location. While the CIFASD has ongoing international recruitment sites, only data collected in United States testing centers were considered in this study to minimize the potential impact of cultural or language bias on neuropsychological tests. Data were analyzed across several sites: Atlanta, Los Angeles, Northern Plains States (seven different communities throughout North Dakota, South Dakota, and Montana), Albuquerque, and San Diego.

Primary caregivers completed specific modules from the clinician-assisted National Institute of Mental Health Diagnostic Interview Schedule for Children-IV on the same day as the neuropsychological battery [C-DISC-4.0; (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000)]. The C-DISC-4.0 is a 90-120 minute computerized structured diagnostic interview based on the DSM-IV, administered to caregivers of children between the ages of 8-17 years old (American Psychiatric Association, 2000; Shaffer, et al., 2000). The C-DISC-4.0 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.

Children with histories of heavy prenatal alcohol exposure were recruited retrospectively and had confirmed histories of heavy prenatal alcohol exposure defined as maternal consumption of more than four alcoholic drinks per occasion at least once per week or at least 14 drinks per week on average repeatedly during pregnancy. Several standard methods were used to confirm prenatal alcohol exposure, including medical history, birth records, social services records, and, when available, maternal report (Mattson, et al., 2010). In order to determine alcohol-related diagnoses, a member of the CIFASD Dysmorphology Core evaluated each study subject using a standardized assessment following the CIFASD Dysmorphology Core diagnostic criteria, which have been published elsewhere (Jones et al., 2006).

Four subject groups were included in this study, two with histories of heavy prenatal alcohol exposure and two without such history. Alcohol-exposed (AE) children were divided into two groups: those who met DSM-IV criteria for an ADHD diagnosis according to the C-DISC-4.0 (AE+; $n = 90$) and those who did not (AE−; $n = 38$). Of the children with histories of heavy prenatal alcohol exposure, 34 (26.5%) met diagnostic criteria for FAS [AE+; $n = 23$ (25.6%), AE−; $n = 11$ (28.9%)]. Children without prenatal alcohol exposure were also divided into two groups. The ADHD clinical comparison group (ADHD; $n = 80$) consisted of children who met DSM-IV diagnostic criteria for ADHD per the C-DISC-4.0. The control group (CON; $n = 136$) consisted of children who did not meet C-DISC-4.0 diagnostic criteria for ADHD. Children who had subclinical symptoms of ADHD, per the C-DISC-4.0,

defined as having more than minimal symptoms, (greater than 3), yet not meeting the threshold of 6 or more symptoms, were excluded from all groups.

The non-exposed comparison groups (ADHD, CON) were screened for prenatal alcohol exposure and were included only if there was less than minimal exposure (defined as one drink per week on average and never more than two drinks on a single occasion) throughout gestation. In addition to group-specific criteria, all subjects had the following exclusion criteria: non-fluent in English, history of significant head injury or loss of consciousness > 30 minutes, adopted from abroad after age 5 or < 2 years before assessment, evidence of other known causes of mental deficiency (e.g. congenital hypothyroidism, chromosomal abnormalities, neurofibromatosis), or psychiatric or physical disability that prevented study completion.

Subjects were administered a comprehensive standardized neuropsychological test battery in a single session by a trained examiner who was blind to subject group. Informed written consent and assent were obtained from all subjects and primary caregivers prior to testing. All children were asked to abstain from medication on the day of testing, however not all subjects were medication naïve and not all were able to abstain during testing. Incentive was provided to both children and caregivers for participation. The Institutional Review Board (IRB) at San Diego State University and other CIFASD sites approved this study.

Procedure

This study utilized three well-regarded and psychometrically sound neuropsychological measures to assess cognitive functioning. See Table 1 for subtest descriptions. Scaled or z-scores based on age were used for all dependent measures.

Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV).—The WISC-IV (Wechsler, 2003) was used to obtain a full-scale IQ (FSIQ) score as well as composite index scores for individual cognitive domains [Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI)].

Delis-Kaplan Executive Functioning System (D-KEFS).—The D-KEFS (Delis, Kaplan, & Kramer, 2001) tasks provide a sensitive and valid approach for evaluating multiple components of executive functioning. The following scaled scores were used as the dependent variables: Design Fluency Switching (DF), Color-Word Interference Inhibition (CWI), Color-Word Interference Inhibition/Switching (CWS), Twenty Questions Test Total Initial Abstraction (TQ), Tower Test Total Achievement (TT), Verbal Fluency Switching (VF) and Trail Making Test Number-Letter Switching (TMT).

Cambridge Neuropsychological Test Automated Battery (CANTAB).—The CANTAB (Cambridge Cognition Limited, 2005) measures various nonverbal components of neuropsychological functioning with an emphasis on executive functioning and has high internal consistency and construct validity (Luciana, 2003). The CANTAB variables were the z-scores from the higher order cognitive subtests [(Delayed Matching to Sample (DMS), Intra-Extra Dimensional Shift Total Errors (IED-TE), IED Stages Completed (IED-SC), and Spatial Working Memory (SWM)].

<u>**Statistical Analysis:**</u> Statistical analyses were conducted using the SPSS statistical package version 19.0 (SPSS, 2010). Demographic data were analyzed using chi-square [sex, race/ethnicity, handedness] and standard analysis of variance (ANOVA) techniques [age and FSIQ]. The following *a priori* data analysis strategy was employed: three separate 2 (AE) ×

2 (ADHD) between-subjects MANCOVAs would be performed on variables from the
WISC-IV, D-KEFS, and CANTAB, respectively, using an alpha of $p = .05$. Pillai's trace
criterion would be used as the omnibus test statistic. We planned to follow up significant
interactions of AE and ADHD using a three-step process: (1) an interaction contrast
(Maxwell & Delaney, 2004) would determine whether the effect of ADHD in exposed
children differed from non-exposed children [(AE+ − AE−) − (ADHD − CON)]; (2) if
significant, the interaction contrast would be followed up using simple effects to reveal the
source of the interaction; (3) finally, because our research question relates to
neuropsychological function of alcohol-exposed children compared to other non-exposed
groups, if the source of the interaction was a difference between AE groups, they would be
compared independently to non-exposed groups (AE+ vs. ADHD, AE− vs. ADHD, AE+−
vs. CON, AE− vs. CON); alternatively, if there was no significant difference between the
AE groups, they would be combined (AE+/−) and compared to non-exposed groups (AE+/−
vs. ADHD, AE+/− vs. CON). These comparisons would utilize a Bonferroni correction at α
=.05/total number of planned contrasts) to control for Type I error. Marginal significance
would be defined as $p < .05$ for the contrasts.

Results

Demographic Information

There were no group differences on age [$F (3, 343) = 1.94$, $p = .122$], handedness [χ^2 ($df =$
$3) = 2.38$, $p = .497$] and ethnicity [χ^2 ($df = 6) = 9.80$, $p = .133$]. However, groups differed
significantly on sex [χ^2 ($df = 3) = 15.69$, $p = .001$], race [χ^2 ($df = 18) = 31.53$, $p = .025$], and
FSIQ [$F (3, 341) = 66.07$, $p < .001$]. Pairwise comparisons indicated that the ADHD group
had significantly more males than the CON ($p = .001$), AE− ($p < .001$), and the AE+ groups
($p = .014$), which did not differ significantly from each other ($p > .112$). As expected, the
ADHD group had significantly more male subjects compared to the other groups, which is
representative of the ADHD clinical population as there is an expected ratio of 1:3 males in
non-exposed children with ADHD (Cantwell, 1996; Graetz, Sawyer, Hazell, Arney, &
Baghurst, 2001; Merikangas et al., 2010). The AE− group had significantly fewer White
subjects compared to the CON ($p < .001$), ADHD ($p = .047$), and AE+ groups ($p = .047$),
which did not differ from each other ($p > .232$). For FSIQ, using Tukey's HSD, the CON
group had significantly higher ($p < .001$) scores than the AE+, AE−and ADHD groups. The
AE+ group had significantly lower FSIQ than the ADHD group ($p < .001$) but there was no
significant difference between AE groups ($p = .152$), or the AE− and ADHD groups ($p = .$
540). Demographic information is presented in Table 2.

Additionally, as this was a multi-site study, we assessed if there were site differences for
demographic variables. We found that there were significant site differences for age and
race (ps < .034). Further, to ensure that site did not affect our results, we re-ran the analyses
using a 2 (AE: Exposed, Non-Exposed) × 2 (ADHD status: Diagnosed, Not Diagnosed) × 5
(Site: Albuquerque, Atlanta, Los Angeles, Northern Plains States, San Diego). The three-
way interaction was not significant ($p = .644$) and the main effects and interaction effects
remained the same. Therefore, we are able to confirm that there was no difference for the
main effects of exposure or ADHD across sites.

Additional Covariates—Given the possible influence of demographic differences (i.e.,
sex, race, IQ, age) on the dependent variables, the inclusion of potential covariates was
considered. Using bivariate correlations, we found that race was not significantly associated
with any of the outcome variables, ps =.224, and therefore was not considered an
appropriate model covariate. Sex was significantly related to outcome variables ($p <.001$).
Follow-up bivariate correlations revealed that sex was not associated with any CANTAB

variables (p = .330) but was significantly correlated with the WISC-IV and D-KEFS variables ($p < .001$) and therefore was considered a covariate in those analyses. Age was significantly associated with all outcome variables ($p < .001$). Follow-up bivariate correlations revealed that age was negatively associated with WISC (p =.032) and D-KEFS and positively associated with the CANTAB ($p < .001$) variables and was used as a covariate in those analyses. Although groups also differed on IQ, the extant literature illustrates the analytical, statistical and theoretical problems of covarying for IQ for neurodevelopmental disorders (Dennis et al., 2009). Furthermore, our interest in the components of IQ as variables in this study, supports not using it as a covariate.

Neuropsychological Measures

Three 2 (AE) × 2 (ADHD) between-subjects MANCOVAs were performed separately for WISC-IV, D-KEFS, and CANTAB variables. Average WISC-IV, D-KEFS, and CANTAB scores for each group are displayed in Table 3.

WISC-IV—For WISC-IV variables, there were significant multivariate effects for both independent variables: AE [F (4, 333) = 17.78, $p < .001$, partial η^2 = 0.176] and ADHD [F (4, 333) = 11.96, $p < .001$, partial η^2 = .126], and the covariates of Sex [F (4,333) = 8.88, $p < .001$, partial η^2 = .096] and Age [F (4,333) = 2.68, p =.032), partial η^2 = .031]. The AE × ADHD interaction was also significant [F (4, 333) = 3.33, p = .011, partial η^2 = .038]. To probe the significant multivariate effects, we examined the between-subjects effects for each individual dependent variable. There were significant main effects of AE and ADHD diagnosis ($ps < .001$) on each of the WISC-IV index composite scores; Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed indices (VCI, PRI, WMI, PSI). Heavy prenatal alcohol exposure was associated with lower WISC-IV scores, regardless of ADHD diagnosis. Also, children with ADHD exhibited lower scores on WISC-IV scores than children without ADHD, across levels of AE. The AE × ADHD diagnosis interaction effects were statistically significant for VCI (p = .005) and PRI (p =.001), indicating that the effect of AE on VCI and PRI differed depending on the presence or absence of ADHD. See Table 4 and Figure 1.

The planned interaction contrast indicated a significant difference ($ps < .006$) between the differences of (AE+ and AE−) and (ADHD and CON) for both VCI and PRI. Simple effects indicated that the interaction contrast was driven by the difference of ADHD and CON (ps <.001; ADHD < CON); there were no differences between the AE+ and AE− group on either VCI or PRI ($ps > .216$), which supports the use of the combined AE+/− group in subsequent analyses. Importantly, the proportion of children with ADHD (70%) in this combined group was consistent with previous studies of children with FASD (Fryer, et al., 2007; Landgren, et al., 2010). This combined AE+/− group performed significantly worse than the ADHD group on both VCI ($p < .001$) and PRI (p = .009). Additionally, the combined AE+/− performed significantly worse than the control group on both measures ($ps < .001$). See Table 5.

D-KEFS—There were significant multivariate effects for AE [F (7, 311) = 11.02, $p < .001$, partial η^2 = .199], ADHD [F (7, 311) = 3.43, p = .001, partial η^2 = .072], and the covariates of Sex [F (7, 313) = 3.96, $p < .001$, partial η^2 = .082] and Age [F (7,311) = 4.72, $p < .001$, partial η^2 = .096) for D-KEFS subtest scores. The AE × ADHD diagnosis interaction was also significant [F (7, 311) = 2.52, p = .016, partial η^2 = .054]. To probe the significant multivariate effects, we examined between-subjects effects on each individual dependent variable. There were statistically significant main effects for AE and ADHD on all D-KEFS subtest scores with the exception of Tower Test (TT), which, while significant for ADHD (p = .002), was not significant for AE (p = .088). Thus, children with histories of prenatal

alcohol exposure had significantly lower scores than the non-exposed groups on all executive functioning measures, except on TT, regardless of ADHD diagnosis. Also, children with ADHD exhibited lower scores on the D-KEFS than children without ADHD, regardless of AE history. The AE × ADHD diagnosis interaction effects were statistically significant ($p < .036$) for Design Fluency, Verbal Fluency, and Trail Making (DF, VF, and TM) scaled scores. See **Table 4**. The interaction contrast, (AE+ vs. AE−) vs. (ADHD vs. CON), was statistically significant ($ps < .024$) for all three D-KEFS subtests with significant interactions. Simple effects revealed that there was a significant difference between ADHD and CON on all three D-KEFS tasks ($ps < .001$; ADHD < CON), however there was no difference between the alcohol-exposed groups ($ps > .207$). This indicated the use of a combined AE+/− group that performed marginally worse than the ADHD group on VF ($p = .026$) and did not differ significantly from the ADHD group on any other D-KEFS task ($p > .206$). The AE+/− group performed significantly worse ($p < .001$) than the CON group for DF, VF and TM. See Table 5.

CANTAB—There were significant multivariate effects for AE [$F (4, 302) = 11.36$, $p < .001$, partial $\eta^2 = .131$], ADHD [$F (4, 302) = 6.90$, $p < .001$, partial $\eta^2 = .084$], and the covariate of Age [$F (4, 302) = 22.19$, $p < .001$, partial $\eta^2 = .227$]. The AE × ADHD interaction was also significant [$F (4, 302) = 3.40$, $p = .010$, partial $\eta^2 = .043$]. To probe the significant multivariate effects, we examined the between-subjects effects for each individual dependent variable.. There were statistically significant ($p < .004$) main effects of AE on all CANTAB subtest scores (AE< Non-exposed). There were also statistically significant main effects of ADHD (ADHD < non-ADHD) on SWM and DMS (p .001), but not on IED-SC or IED-TE ($p > .079$). The AE × ADHD interaction effect was statistically significant ($p = .001$) for SWM. See Table 4. The interaction contrast, (AE+ vs. AE−) vs. (ADHD vs. CON), was significant ($p = .001$) for SWM. Simple effects showed that there was no significant difference between the AE+ and AE− ($p = .582$), and that the interaction contrast significant was driven by the difference of ADHD and CON ($p < .001$; ADHD < CON). There was no significant difference ($p = .224$) between the combined AE+/− group and ADHD, however the combined AE+/− group performed significantly worse than the CON group ($p < .001$) for SWM. See Table 5.

Discussion

This study assessed neuropsychological performance in controls and three clinical groups of children: (1) children with histories of heavy prenatal alcohol exposure, (2) non-exposed children diagnosed with ADHD, and (3) children with both prenatal alcohol exposure and ADHD. We sought to examine the relationship between prenatal alcohol exposure and ADHD on neuropsychological performance. Neuropsychological abilities were assessed using a test battery designed to measure general intellectual abilities and executive functioning. As hypothesized, across all neuropsychological domains, the alcohol-exposed children were more impaired than controls, regardless of ADHD diagnosis, and children with ADHD were impaired relative to controls, regardless of exposure history. These findings are consistent with previous studies in AE (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). Furthermore, six tasks showed significant interaction effects of ADHD and prenatal alcohol exposure, including two indices of general intellectual performance (WISC-IV Verbal Comprehension and Perceptual Reasoning), and four measures of executive functioning (D-KEFS Design Fluency, Verbal Fluency and Trail Making; CANTAB Spatial Working Memory).

While we had hypothesized that the combination of multiple risk factors in the AE+ group would result in more severe deficits in the neuropsychological domain, as in recent behavioral studies (Graham, et al., 2012; Ware, O'Brien, et al., 2012), results revealed no

significant differences between the AE+ and AE− groups on any neuropsychological measure. Thus, the presence of an ADHD diagnosis did not have the same impact in the exposed sample as it did in the non-exposed sample. The lack of exacerbated impairments suggests that different mechanisms or risk factors may underlie the behavioral and neuropsychological deficits in children with concomitant AE and ADHD. For example, neural changes resulting from prenatal alcohol exposure may lead to such severe impairment that the co-occurrence of changes associated with concomitant ADHD does not further exacerbate neuropsychological performance (Sonuga-Barke, 2005). Differences could also be due to methodological differences as the behavioral studies were based on parent report measures, whereas the current study assessed neuropsychological performance through direct standardized assessment measures. Possible differences between the groups in access to services, medication, and school placements also may have contributed to the discrepancy.

In support of the previous literature, verbal comprehension and perceptual reasoning performance was impaired in both AE (Aragón et al., 2008; Kaemingk & Halverson, 2000; Kodituwakku, 2007; Mattson, Crocker, et al., 2011; Willoughby, Sheard, Nash, & Rovet, 2008) and ADHD (Andreou, Agapitou, & Karapetsas, 2005; Frazier, Demaree, & Youngstrom, 2004; Pineda, Puerta, Aguirre, García-Barrera, & Kamphaus, 2007). However, we found that alcohol-exposed children, regardless of ADHD diagnosis, presented with more severe verbal comprehension and perceptual reasoning deficits than non-exposed children with ADHD. This pattern of impairment (AE+/− < ADHD < CON) has not been specifically reported for these measures but is consistent with previous comparisons of visuospatial reasoning (Coles, et al., 1997) and verbal learning (Crocker, et al., 2011), and both domains have been consistently found to be severely impaired in alcohol-exposed children (for review, see Mattson, Crocker, et al., 2011). Spatial processing is considered a central component of the FASD neurobehavioral profile (Mattson et al., 2010) and is deficient in children with FASD even when compared to an IQ-matched comparison group (Carmichael Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998). There is also convergent evidence for diffuse verbal deficits in the FASD population including deficits in expressive and receptive language (Adnams et al., 2007; McGee, Bjorkquist, Riley & Mattson, 2009; Wyper & Rasmussen, 2011), word comprehension (Conry, 1990; LaDue, Streissguth, & Randels, 1992; Mattson & Riley, 1998) as well as grammatical and semantic impairments (Becker, Warr-Leeper, & Leeper, 1990). Conversely, verbal comprehension and perceptual reasoning are not considered core deficits for subjects with ADHD, although they are impaired on all of these domains compared to controls (Ek et al., 2007; Frazier, et al., 2004; Mayes & Calhoun, 2004; Wechsler, 2003).

Children with alcohol exposure and children with ADHD were similarly impaired compared to controls on all other neuropsychological measures related to executive functioning (WISC-IV Working Memory and Processing Speed, all D-KEFS and CANTAB subtests). Executive dysfunction represents a hallmark deficit for both children with FASD (Mattson, Crocker, et al., 2011) and non-exposed children with ADHD (Barkley, 1997; Nigg, 2005). The similar deficits demonstrated by the clinical groups might be a result of a shared core deficit of higher order processing (Mattson, Crocker, et al., 2011). Relative weaknesses in executive functioning in non-exposed children with ADHD may bring them into the range of deficits exhibited by the alcohol-exposed children. In spite of the similar deficits noted in the clinical groups, Mattson, et al. (2013) reported that variables from the CANTAB and D-KEFS could be used to differentiate subjects with prenatal alcohol exposure from ADHD with 73.9% clarification accuracy. Thus, while the within-group variability of executive function performance is sufficient to accurately distinguish these clinical conditions (Mattson, et al., 2013), the current results support the use of other, potentially more sensitive measures for heavy prenatal alcohol exposure, such as verbal comprehension and perceptual

reasoning performance, to differentiate the clinical groups. Importantly, the lack of significant group differences in executive function ability does not obviate the need for intervention and remediation as they are both impaired compared to controls. Of note, verbal fluency was an important variable in distinguishing AE from ADHD in the 2013 study (Mattson, et al., 2013). In the current study, while EF measures overall were not significantly different between the clinical groups, performance on verbal fluency was marginally significant, given our adjusted *p*-value. This provides further evidence that verbal measures may be more sensitive to heavy prenatal alcohol exposure.

Strengths and Limitations

Despite having clinically relevant and significant findings, our results should be considered in the context of important limitations. We did not examine the relationship between neuropsychological performance and IQ scores. Unfortunately, the options for dealing with expected IQ differences (e.g., matching groups or covarying IQ in analyses), result in additional analytical and theoretical problems, such as producing meaningless results if the covariate is intrinsic to group membership, creating statistically overcorrected results, and decreasing the generalizability of results (Dennis, et al., 2009).

Furthermore, our analyses included index scores that contribute to an IQ score, which obviates the issue of covarying. An additional limitation to our study was the relatively large age range. While a large age range may increase variability and perhaps oversimplify important developmental changes, it allowed us to include a larger sample size, adding statistical power to our study. We addressed this limitation thoroughly, as our groups were equivalent on age, all measures had age-standardized scaled scores, and age-related variance was accounted for by including age as a covariate in the analyses. Demographic variables related to neuropsychological and executive function such as race, ethnicity and sex were evaluated as covariates in the current analysis, however socioeconomic status (SES) was not as it was not included during the implementation of the international CIFASD methodology. Further research would benefit from an investigation of home environment and SES on neurocognition in children with FASD.

Children were asked to abstain from medication during the testing, however not all children were able to and medication effects may have contributed to the results. Not excluding children based on medication status or concurrent psychopathology facilitates the generalizability of these findings across the population of children with heavy prenatal alcohol exposure. Nevertheless, the current study has notable strengths including its comparisons between alcohol-exposed children with and without ADHD and the use of a clinical contrast group. Furthermore, the sample size, collected from centers across the United States, is quite large and representative, allowing for greater generalizability of our results.

Implications and Future Directions

These data demonstrate differential behavioral and neuropsychological outcomes resulting from concomitant heavy prenatal alcohol exposure and ADHD. Although, as evidenced in our sample, alcohol-affected children are more likely to have ADHD than the general population (Fryer, et al., 2007; Landgren, et al., 2010; Rasmussen, et al., 2010), there was no evidence of exacerbated cognitive deficits for alcohol-exposed children with ADHD compared to those without ADHD as seen in previous studies of behavior ratings. Therefore, this study supports the current methodological standard of combining AE+ and AE− into one alcohol-exposed group regardless of ADHD status. Results further indicate that cognitive findings from the last several decades of research in heavy prenatal alcohol exposure apply to children across the spectrum of FASD, regardless of concomitant ADHD.

Our results support and extend the prior literature demonstrating numerous shared deficits for both FASD and ADHD compared to controls (set shifting, complex motor skills, social skills, static balance, communication skills, parent reports of behavior), which hinders diagnostic specificity (Mattson, Crocker, et al., 2011; Mattson & Riley, 2011). However, in spite of these similarities, the presence of an ADHD diagnosis did not have the same impact on neuropsychological functioning in the exposed sample as it did in the non-exposed sample emphasizing that these two clinical conditions are not identical. We found that certain measures may be more sensitive in differentiating between ADHD and FASD. These results add to previous reports demonstrating differences between FASD and ADHD on attention (Coles, et al., 1997; Kooistra, Crawford, Gibbard, Kaplan, & Fan, 2011), response inhibition (Burden, et al., 2010), motor response time and balance (Kooistra, et al., 2010), overall deficits in letter fluency (Vaurio, et al., 2008), verbal learning and memory (Crocker, et al., 2011), and mathematics (Jacobson, Dodge, Burden, Klorman, & Jacobson, 2011). Further, this study indicates that measures of verbal comprehension and perceptual reasoning are also sensitive assessment measures for distinguishing alcohol-exposed children from non-exposed children with ADHD.

There are definite clinical benefits to accurately distinguishing children with FASD from non-exposed children with ADHD. To this end, successful identification of distinct clinical populations requires greater understanding of the complex relationship between ADHD and neuropsychological performance in children with and without prenatal exposure. There is evidence of greater positive outcomes for children with prenatal alcohol exposure who are identified and treated early (Adnams, et al., 2007; Paley & O'Connor, 2009; Yazdani, Motz, & Koren, 2009) and certain medications have different treatment efficacies between alcohol-exposed and non-exposed children with ADHD (Coles, et al., 1997; Oesterheld et al., 1998). Clinically, these findings demonstrate task-dependent patterns of impairment across clinical groups, with alcohol-exposed children demonstrating more severe verbal and perceptual deficits compared to children with ADHD. Both groups demonstrated executive function deficits. Further investigation of the underlying mechanisms of these domains may facilitate better characterization of the clinical similarities and differences between groups and lead to targeted and specialized interventions for these highly prevalent clinical groups.

Acknowledgments

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Verbal Comprehension

Perceptual Reasoning
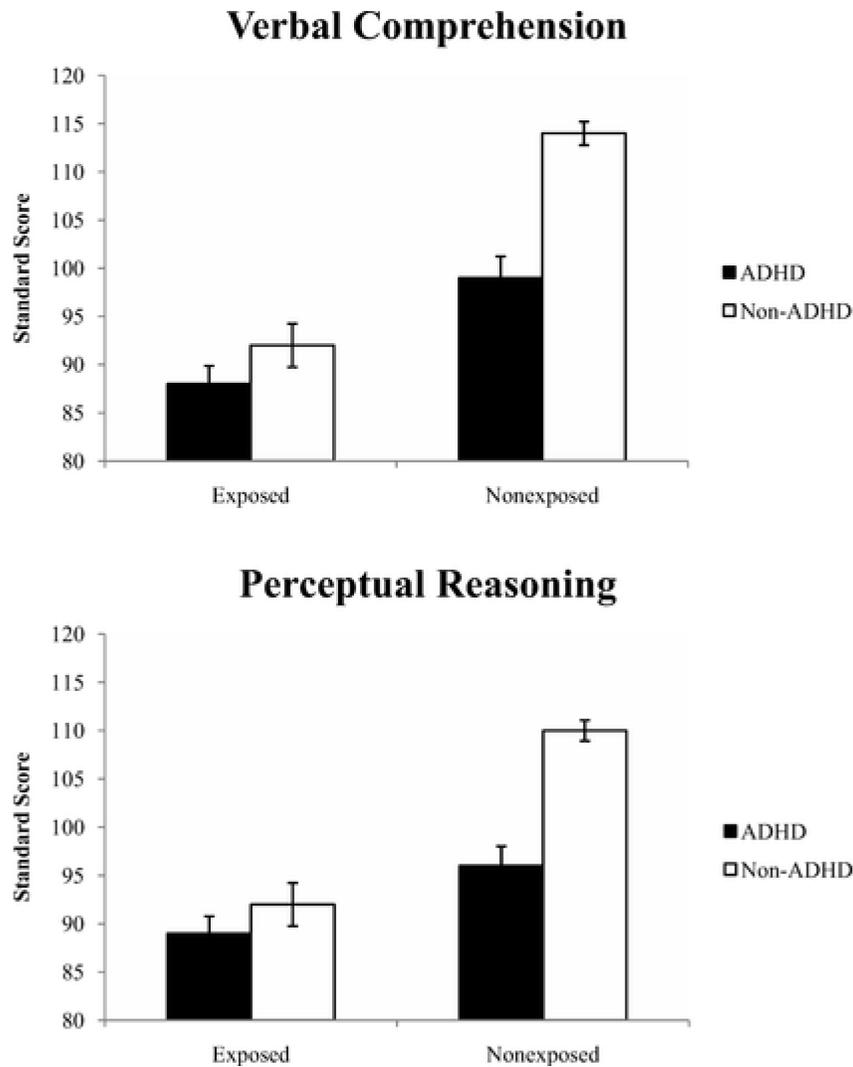
Figure 1.
Example of neuropsychological subtests with an Alcohol Exposure (AE) × Attention-Deficit/Hyperactivity Disorder status (ADHD) interaction. Errors bars indicate standard error of the mean. The top panel illustrates the AE × ADHD interaction for WISC-IV Verbal Comprehension Index and the bottom panel illustrates the AE × ADHD interaction for WISC-IV Perceptual Reasoning Index. For both measures, the AE+/− group performed significantly worse than the ADHD group and both clinical groups perform significantly worse than controls. There are four other significant interactions of AE and ADHD, which are not pictured, where the AE+/− group was not significantly different from the ADHD group (see Table 3).

Table 1

Descriptions of Neuropsychological Measures

Measure	Subtest	Description
WISC-IV	Verbal comprehension	Index score of three components (vocabulary, similarities, comprehension) assessing verbal concept formation and reasoning.
	Perceptual reasoning	Index score of four components (block design, picture concepts, matrix reasoning, picture completion) assessing visuospatial processing, cognitive flexibility, and nonverbal reasoning.
	Working memory	Index score of three components (digit span, letter-number sequencing, arithmetic) assessing attention, concentration, mental control and working memory.
	Processing speed	Index score of three components (coding, symbol search, cancellation) assessing speed of processing visual stimuli.
D-KEFS	Design fluency switching	Scaled score of switching condition requiring rule change between production of design using a series of dots assessing fluency in generating visual designs, rule following and problem solving.
	Color-word interference inhibition	Scaled score of time taken to read the ink color a word is printed in (different from the actual word). while inhibiting the natural verbal reading response assessing cognitive flexibility and inhibitory control.
	Color-word interference inhibition/switching	Scaled score of time taken to complete switching between inhibitory and noninhibites responses of color naming and word reading assessing cognitive flexibility and inhibitory control.
	Twenty questions	Scaled score of the quality of an intial question asked to reduce potential response options, assessing logical thinking, hypothesis testing and deduction.
	Tower test	Scaled score of the total number of rule violations per item ratio, assessing spatial planning, rule learning, inhibition and the maintenance of a cognitive set.
	Verbal fluency category switching	Scaled score of total number of correct words produced during switching task, regardless of switching accuracy assessing verbal production, simultaneous processing, retrieval and expressive language.
	Trail making switching	Scaled score of time taken to properly connect alternating sequences of numbers and letters, assessing for visual-motor cognitive flexibility.
CANTAB	Delayed matching to sample	Z-score of percent correct matching of a novel pattern shown to one of four response options shown at 4000 ms or 12,000 ms delay assessing short-term and long-term visual and spatial memory.
	Intra-extra dimensional shift total errors	Z-score total numbers of errors made by failure to adjust to the novel conditions and properly attend to the correct features of shapes and lines assessing cognitive flexibility, discrimination, and attention shifting.
	Intra-extra dimensional shift stages completed	Z-score of number of rule change stages completed on a measure requiring adaptation to a series changing conditions assessing cognitive flexibility, visual discrimination, and attention shifting.
	Spatial workin memory	Z-score of total number of errors counted as returning to a loction where a stimulus was previously found on a screen where one goes to novel locations to determine the correst responses assessing cognitive flexibility, rule learning, and spatial working memory.

Note. WISC-IV = Wechsler Intellignece Scale For Children, Fourth Edition; D-KEFS = Delis-Kaplan Executive Function System; CANTAB = Cambridge Neuropsychological Test Automated Battery.

Table 2

Participant Characteristics

Demographic variable	Exposed		Nonexposed		
	AE+ (*n* = 90)	AE− (*n* = 38)	ADHD (*n* = 80)	CON (*n* = 136)	Parametric statistics
Handedness [*n* (% Right)]	78(86.7)	35(92.1)	72(90.0)	126(92.6)	
FAS [*n* (%)]	23(25.6)	11(28.9)	0(0.0)	0(0.0)	
Sex [*n* (% Females)]*	36(40.0)	21(55.3)	18(22.5)	62(45.6)	ADHD < AE+, AE−, CON
Race [*n* (%White)]*	57(63.3)	14(36.8)	53(66.3)	94(69.1)	AE− < CON, ADHD
Ethnicity [*n* (% Hispanic)]	8(8.9)	7(18.4)	20(25.0)	28(20.6)	
Age [*M* (*SD*)]	12.4(2.4)	12.6(2.6)	11.7(2.5)	12.5(2.6)	
FSIQ [*M* (*SD*)]*	82.44(17.497)	88.71(14.108)	92.77(18.535)	110.31(11.860)	ADHD, AE−, AE+, < CON; AE+ < ADHD
CIFASD Site [*n* (%)]					
Albuquerque	7(7.8)	2(5.3)	11(13.8)	20(14.7)	
Atlanta	15(16.7)	12(18.5)	19(23.8)	19(14.0)	
Los Angeles	17(18.9)	10(26.3)	2(2.5)	18(13.2)	
Northern Plains States	13(14.4)	5(13.2)	9(11.3)	18(13.2)	
San Diego	38(42.2)	9(23.7)	39(48.8)	61(44.9)	

Note. Demographic information for the four groups: alcohol-exposed children with ADHD(AE+), and without ADHD(AE−), nonexposed children with ADHD (ADHD), and typically developing controls (CON). CIFASD = Collaborative Initiative on Fetal Alcohol Spectrum Disorders.

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

Table 3

Performance Across Groups

Measure [*m (SD)*]	Exposed		Nonexposed		
	AE+ (*n* = 90)	AE− (*n* = 38)	ADHD (*n* = 80)	CON (*n* = 136)	Planned comparisons
WISC-IV, Composite scores					
Verbal comprehension[*]	88.07(17.75)	92.08(13.82)	98.92(19.77)	113.98(14.18)	AE+/− < ADHD < CON
Perceptual resoning[*]	88.89(16.91)	91.87(13.82)	96.28(17.96)	110.26(12.50)	AE+/− < ADHD < CON
Working memory	82.25(15.85)	92.00(13.67)	91.10(16.19)	104.63(12.04)	
Processing speed	81.18(15.69)	87.18(14.18)	86.77(15.13)	98.33(13.54)	
D-KEFS, Scaled scores					
Design fluency[*]	7.89(2.80)	8.55(2.51)	8.78(3.28)	11.10(3.08)	AE+/−, ADHD < CON
Color-word inhibition	7.45(3.60)	8.82(3.04)	9.00(3.67)	10.80(2.41)	
Color-word inhibition/switching	8.05(3.90)	8.86(3.09)	9.47(3.20)	11.03(2.37)	
Twenty questions	7.88(2.62)	8.29(2.40)	9.28(3.54)	11.12(3.25)	
Tower task	8.03(2.98)	9.18(2.77)	8.65(3.28)	10.24(2.48)	
Verbal fluency[*]	7.89(3.60)	7.74(2.91)	8.89(3.020	11.61(3.17)	AE+/−, ADHD < CON
Trail making[*]	6.63(4.03)	7.58(3.49)	7.69(4.58)	10.71(2.60)	AE+/−, ADHD < CON
CANTAB, z-scores					
Delayed matching to sample	−0.18(1.13)	0.37(1.04)	0.11(0.97)	0.76(0.76)	
IED total errors	−0.20(1.14)	−0.20(0.92)	−0.04(1.08)	0.39(1.08)	
IED stages completed	0.17(0.75)	0.03(1.08)	0.21(0.87)	0.48(0.66)	
Spatial working memory[*]	−0.16(0.76)	−0.07(0.92)	0.02(0.77)	0.72(0.69)	AE+/−, ADHD < CON

Note. Mean scores are reported above for the four groups [children with heavy prenatal alcohol exposure and ADHD(AE+), chilfren with heavy prenatal alcohol exposure without ADHD(AE−), nonexposed children with ADHD (ADHD), and controls (CON)]. WISC-IV = Wechsler Intelligence Scale for Children, Fourth Edition; D-KEFS = Delis-Kaplan Executive Function System; CANTAB = Cambridge Neuropsychological Test Automated Battery; IED = Intra-Extra Dimensional Shift. AE+/− = combined alcohol-exposed group.

[*] Subsets with significant AE × ADHD interactions.

Table 4

Main and Interaction Effects of ADHD and Alcohol Exposure (AE, ADHD, AE × ADHD)

	AE main effect			ADHD main effect			AE × ADHD interaction		
	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
WISC-IV (overall) $F(4,333)$	17.78	<.001	.176	11.96	<.001	.126	3.33	.011	.038
Verbal comprehension $F(1,336)$	63.73	<.001	.159	23.50	<.001	.065	8.11	.005	.024
Perceptual reasonig $F(1,336)$	44.18	<.001	.116	25.02	<.001	.069	10.31	.001	.030
Working memory $F(1,336)$	37.58	<.001	.101	44.81	<.001	.118	1.29	.257	.004
Processing speed $F(1,336)$	26.97	<.001	.074	20.22	<.001	.057	2.84	.093	.008
D-KEFS overall $F(7,311)$	11.02	<.001	.199	3.43	.001	.072	2.52	.016	.054
Design fluency $F(1,317)$	22.76	<.001	.067	8.60	.004	.026	4.44	.036	.014
Color-word inhibition $F(1,317)$	19.35	<.001	.058	11.70	.001	.036	0.64	.424	.002
Color-word switching $F(1,317)$	21.90	<.001	.065	7.83	.005	.024	1.25	.264	.004
Twenty question $F(1,317)$	31.68	<.001	.091	5.24	.023	.046	2.34	.127	.007
Tower task $F(1,317)$	2.92	.088	.009	9.73	.002	.030	0.62	.430	.002
Verbal fluency $F(1,317)$	40.51	<.001	.113	5.35	.021	.017	13.15	<.001	.040
Trail making $F(1,317)$	19.78	<.001	.059	14.31	<.001	.043	6.87	.009	.021
CANTAB overall $F(4,302)$	11.36	<.001	.131	6.90	<.001	.084	3.40	.010	.043
Delay matching to sample $F(1,306)$	13.45	<.001	.042	21.60	<.001	.066	0.04	.835	<.001
IED total errors $F(1,306)$	8.48	.004	.027	3.10	.079	.010	0.46	.497	.002
IED stages completed $F(1,306)$	9.79	.002	.031	0.17	.895	<.001	3.55	.061	.012
Spatial working memory $F(1,306)$	41.57	<.001	.120	11.97	.001	.038	10.42	.001	.033

Note. η_p^2 = Partial eta squared effect sizt; WISC-IV = Wechsler Intelligence Scale for Children, Fourth Edition; D-KEFS = Delis-Kaplan Executive Function System; CANTAB = Cambridge Neuropsychological Test Automated Battery; IED = Intra-Extra Dimensional Shift.

Table 5

Interaction Contrast, Simple Effects, and Planned Comparison Contrasts Between Groups

Variable	Interaction contrast (AE+ vs. AE−) − (ADHD vs. CON)			Simple effects				Planned comparisons			
				AE+ vs. AE−		ADHD vs. CON		AE+/− vs. ADHD		AE+/− vs. CON	
	Contrast estimate	F	p	F	p	F	p	t	p	t	p
Verbal comprehension	11.042	7.758	.006	1.543	.216	41.854	<.001	3.607	<.001*	11.180	<.001*
Perceptual reasoning	11.007	9.077	.003	.919	.339	45.003	<.001	2.608	.009*	10.092	<.001*
Design fluency	1.616	5.142	.024	1.598	.209	26.927	<.001	1.268	.206	7.427	<.001*
Verbal fluency	2.772	13.028	<.001	.053	.818	38.118	<.001	2.239	.026	9.095	<.001*
Trail making	2.047	5.529	.019	1.610	.207	37.742	<.001	1.085	.279	7.711	<.001*
Spatial working memory	.613	11.240	.001	.305	.582	45.573	<.001	1.218	.224	8.504	<.001*

Note. Alcohol-exposed children with ADHD (AE+), and without ADHD (AE−), combined alcohol-exposed group (AE+/−), nonexposed children with ADHD (ADHD), and typically developing controls (CON) for the six subtests for which there was a significant AE × ADHD interaction.

*
Significant planned comparisons using a Bonferroni correction at α < .025 (.05/2).