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Relation Between Oppositional/Conduct Behaviors and Executive Function Among Youth with Histories of Heavy Prenatal Alcohol Exposure

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Abstract

Background: Youth with heavy prenatal alcohol exposure have high rates of behavioral concerns and psychopathology, including increased oppositional and conduct behaviors. The relation between those concerns and executive function (EF) deficits is unknown. We investigated the association of oppositional and conduct behavior and EF in adolescents to inform targeted intervention.

Methods: Subjects ($N=267$) ages 10–17y comprised three groups: alcohol-exposed with oppositional/conduct behaviors (AE+), alcohol-exposed without oppositional/conduct behaviors (AE-), and controls (CON). Group differences on direct neuropsychological (D-KEFS) and indirect parent-report (BRIEF) EF measures were tested with MANCOVAs, followed by univariate ANOVAs and pairwise comparisons. The contribution of ADHD within the AE groups was assessed in secondary analyses.

Results: On the D-KEFS, there was an omnibus main effect of Group, with significant main effects on 3 of 6 variables (CON>AE+, AE-). Within the AE groups, ADHD did not alter the results. On the BRIEF, there was an omnibus significant main effect of Group, with significant main effects on all scales (CON<AE-<AE+). Within the AE groups, the AE+ group had higher

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BRIEF scores (i.e., more difficulty) than the AE- group on 4 of 8 subscales when accounting for presence of ADHD.

Conclusions: Executive function deficits in youth with histories of prenatal alcohol exposure were confirmed using direct and indirect measures. Oppositional/conduct behaviors related to EF deficits on indirect but not direct EF measures. Greater understanding of the contribution of concurrent psychopathology to long-term outcomes for alcohol-exposed youth requires further investigation.

Keywords

Executive function; fetal alcohol spectrum disorders (FASD); fetal alcohol syndrome (FAS); neurobehavioral profile

Introduction

Prenatal alcohol exposure can result in clinically significant cognitive and behavioral deficits, including impairment in executive function and increased rates of psychopathology (Mattson et al., 2011, Riley et al., 2011). The range of effects resulting from prenatal alcohol exposure falls on a continuum known as fetal alcohol spectrum disorders (FASD). Recent prevalence estimates suggest FASD may affect as many as 2–5% of school age children (May et al., 2014, May et al., 2015, May et al., 2018) resulting in a serious public health issue.

Executive function (EF) is one of the most robust areas of weakness found in prenatal alcohol exposure (Kodituwakku & Kodituwakku, 2014, Mattson et al., 2011, Paolozza et al., 2014, Rasmussen et al., 2013, Ware et al., 2012). Executive functions comprise top-down cognitive processes that facilitate decision making (Willcutt et al., 2005) and can be measured through direct assessment with the child (neuropsychology testing) or parent-report (Doyle & Mattson, 2015). Youth with prenatal alcohol exposure demonstrate deficits on several aspects of executive functioning as measured by neuropsychological assessment, including cognitive flexibility, set shifting, and spatial working memory (Mattson et al., 2013). These deficits are evident above and beyond what would be expected based on overall lower intellectual functioning (Connor et al., 2000). On parent-report questionnaires, parents of youth with prenatal alcohol exposure report significantly worse behavioral executive function abilities compared to non-exposed youth (Nguyen et al., 2014, Stevens et al., 2013) with the greatest impairment in problem-solving and inhibitory control (Nguyen et al., 2014). In addition to deficits in executive function, adolescents with prenatal alcohol exposure also have significantly higher rates of psychopathology (Burd et al., 2003, Disney et al., 2008, D’Onofrio et al., 2007, Fryer et al., 2007, Kodituwakku & Kodituwakku, 2014, Raldiris et al., 2014, Steinhausen & Spohr, 1998). Disorders involving oppositional and conduct behaviors, such as oppositional defiant disorder (ODD) and conduct disorder (CD), are some of the most functionally impairing and are often associated with incarceration and negative outcomes.

In non-exposed populations, deficits or weaknesses in executive function abilities, such as inhibitory control, are often seen in disorders associated with oppositional and conduct

behaviors (e.g., aggressive behavior, argumentative behavior, vindictive behavior) (Carter Leno et al., 2017, Giancola et al., 1998, Hurt & Naglieri, 1992, Kusché et al., 1993, Matthys et al., 2013). However, the specificity of these relations remains largely unknown (Lueger & Gill, 1990). Often there are numerous other variables that can contribute to EF deficits and oppositional/conduct behaviors including attention-deficit/hyperactivity disorder (ADHD) symptomology, which is also related to EF deficits (Sergeant et al., 2002).

Youth with adverse life events and various prenatal risk factors (e.g., low birth weight; Noordermeer et al., 2017) are at greater risk for EF deficits and ODD/CD. It follows that individuals with histories of prenatal alcohol exposure are at very high risk for externalizing and other behavioral disorders (e.g., ADHD, ODD/CD) as well as weaknesses in executive function (Burd et al., 2003, Disney et al., 2008, D'Onofrio et al., 2007, Fryer et al., 2007, Kodituwakku & Kodituwakku, 2014, Raldiris et al., 2014, Steinhausen & Spohr, 1998). While deficits in EF appear to have an inherent relation with oppositional and conduct behaviors (e.g., poor self-monitoring, decreased impulse control), the association has not been fully elucidated. Further, the effect of comorbid factors that may influence or exacerbate the relation, such as prenatal alcohol exposure or ADHD, has not been assessed.

Among other neurodevelopmental disorders (e.g., ADHD) the presence of ODD/CD does not appear to significantly alter performance on direct neuropsychological measures of executive functioning (Antonini et al., 2015, Ezpeleta and Granero, 2015). Likewise, for externalizing behavioral disorders (i.e., ODD, CD), EF deficits as measured with direct neuropsychological measures is specific to those individuals with ADHD rather than ODD/CD (Clark et al., 2000, Skogan et al., 2014). In contrast, others have suggested certain directly-measured executive function deficits (e.g., risky decision-making) are specific to ODD/CD independent of ADHD (Hobson et al., 2011).

On indirect questionnaires, parents of youth with comorbid ADHD and ODD/CD report greater impairment on behavioral measures of executive function than youth with ADHD only, though performances on neuropsychological measures of executive function are similar (Barnett et al., 2009, Qian et al., 2010). While the relation of oppositional/conduct behaviors on behavior or cognition in youth with prenatal alcohol exposure is not known, a similar result has been noted with regards to ADHD in this population. Youth with prenatal alcohol exposure and ADHD have greater executive function deficits than those without ADHD when rated by parents (Nguyen et al., 2014) but this pattern is not apparent on neuropsychological measures of executive function (Glass et al., 2013, Nguyen et al., 2014). Whether the presence of oppositional/conduct behaviors alters the relation between prenatal alcohol exposure and executive function remains unknown.

In this study, we examined the relation between oppositional/conduct behaviors and alcohol exposure on direct (neuropsychological assessment) and indirect (parent report) measures of EF. Results will provide further clarity regarding the specific neurobehavioral profile of FASD and highlight behavioral impairment evidenced by youth with prenatal alcohol exposure that can significantly affect every day functioning. Given that the additional presence of ADHD is related to behavioral executive function but not neuropsychological performance among this population (Glass et al., 2013, Ware et al., 2013), we expect the

same pattern of results when assessing oppositional/conduct behaviors. Specifically, we hypothesized that relative to the control group, the presence of oppositional/conduct behaviors in the alcohol-exposed subjects would be associated with greater impairment on parent-report of executive function but not on direct assessment (i.e., neuropsychological measures) of executive function. In secondary analyses, we also investigated whether presence of ADHD significantly altered any relations between oppositional/conduct behaviors and executive function.

Materials and Methods

General Methods

Data were collected as part of the third phase of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD III) multisite study. Participants ($N = 267$) were 10–17 years of age ($M = 13.1$). Parents or caregivers completed questionnaires while participants were administered a standardized neuropsychological battery over one 3-hour session. The General Conceptual Ability (GCA) index score from the Differential Ability Scales – Second Edition (DAS-II; Elliott, 2007) was used to obtain an estimate of general intellectual ability. CIFASD methodology has been described previously (Mattson et al., 2010). Participants were tested at four sites: (1) the Center for Behavioral Teratology at San Diego State University, (2) The University of Minnesota FASD Program, (3) The Marcus Institute at Emory University, and (4) the Children's Hospital at the University of Southern California. Recruitment took place through clinical and community referral, including professional referrals, advertisements, schools, and community outreach. All caregivers and participants provided informed consent and assent prior to study participation. Financial incentive was provided to both caregivers and participants. The Institutional Review Board at San Diego State University and other sites approved study procedures.

Subjects

Subjects (age 10–17 years) comprised three groups: alcohol-exposed youth with oppositional/conduct behaviors (AE+, $n = 102$), alcohol-exposed youth without oppositional/conduct behaviors (AE-, $n = 45$), and typically developing controls (CON, $n = 120$). Documentation of alcohol exposure and oppositional/conduct behaviors is described below.

Alcohol Exposure.—Subjects in the alcohol-exposed groups (AE+, AE-) had confirmed histories of heavy prenatal alcohol exposure defined as a pattern of heavy or binge drinking at any point in pregnancy. Heavy or binge drinking was evidenced by maternal consumption of an average of >13 drinks per week or >4 drinks per occasion across pregnancy (Jones et al., 2006, Mattson et al., 2010). Direct maternal report was not available for all subjects. In cases where direct maternal report was not available, a review of medical, social services, or court records was required. In such instances, subjects were included in the alcohol-exposed groups if there was documentation of alcohol abuse or dependence in the biological mother or if exposure was suspected and the child met criteria for fetal alcohol syndrome (FAS). Within the AE+ group, 33.3% of subjects were direct report (i.e., biological mother) and

66.7% of subjects were collateral report. Within the AE- group, 26.7% of subjects were direct report and 73.3% of subjects were collateral report.

Oppositional/Conduct Behaviors.—Presence of symptoms associated with psychiatric conditions (e.g., oppositional or conduct behaviors) was determined using the Computerized Diagnostic Interview Schedule for Children Version IV (C-DISC-4.0; Shaffer et al., 2000). Subjects in the AE+ group evidenced oppositional/conduct behaviors in addition to meeting alcohol-exposed criteria. Based on standardized procedures set forth by the test publisher, presence of oppositional/conduct behaviors was conservatively determined as meeting full or intermediate (i.e., diagnostic criteria not met, but significant symptoms and/or impairment are present) criteria for ODD or CD within the past year or past month per the C-DISC-4.0. Subjects in the AE- group and CON group did not have sufficient ODD or CD behaviors or symptoms to meet the intermediate or full criteria for these disorders. Most had few or no symptoms in this domain.

Control Group.—Subjects in the control group were recruited from the same communities as the alcohol-exposed groups. Subjects were excluded from the CON group if more than minimal prenatal alcohol exposure was suspected or known. Minimal exposure is defined as no more than 1 drink per week on average and never more than 2 drinks per occasion. Subjects were also excluded from the CON group if exposure was unknown. Within the CON group, 91.7% of subjects' exposure histories were direct report and 8.3% were collateral report. Furthermore, per CIFASD inclusion criteria, subjects were excluded from the CON group if parents reported significant behavioral problems or if subjects had previous clinical diagnoses (e.g., ADHD) at time of study enrollment.

Additional Inclusion/Exclusion Criteria.—Other exclusionary criteria for all groups included: being adopted from abroad within two years of participation or after the age of 5, primary language other than English, history of significant head injury and/or loss of consciousness greater than 30 minutes, or presence of a severe psychiatric, physical, or mental disability that prevented participation in the study (e.g., active mania or psychosis, blindness). Subjects completed a physical examination by an expert dysmorphologist to determine presence of FAS and other alcohol-related diagnoses based upon CIFASD criteria (Jones et al., 2006, Mattson et al., 2010).

Measures

Measures from the larger CIFASD III test battery were selected to assess the relation between co-occurring oppositional/conduct behaviors and prenatal alcohol exposure on executive function abilities, assessed both by neuropsychological testing and parent-report. Selected measures are described below.

Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001).—The D-KEFS is a widely used collection of neuropsychological tests that measure various aspects of executive function ability. All D-KEFS scores are scaled scores ($M = 10$; $SD = 3$) with lower scores indicating weaker performance.

Three conditions from the Trail Making Test (i.e., Number Sequencing, Letter Sequencing, Number-Letter Switching) were included in analyses. For the Number Sequencing and Letter Sequencing tasks, participants are asked to connect dots with numbers or letters, respectively, in order. For the Number-Letter Switching task, participants are asked to alternate connecting numbers and letters in order. These tests measure one's fluency, inhibitory control, and cognitive set-shifting abilities. Scaled scores from each condition were included in analyses.

Additionally, the Twenty Questions Test was selected as a measure of higher-level verbal executive functioning skills. The Twenty Questions Test measures abstract reasoning, problem solving, and planning. This test requires participants to ask yes/no questions to identify the object that the examiner has selected with the goal of asking the fewest number of questions. The Initial Abstraction, Total Questions Asked, and Total Weighted Achievement scaled scores were included in analyses. The Initial Abstraction score measures the number of items eliminated with the participant's first question. The Total Questions Asked score measures the total number of questions required for the participant to guess the object. The Total Weighted Achievement score reflects the participant's ability to simply guess the correct answer with fewer questions. As such, bonus points are awarded in a reverse U-shape curve, with fewer points awarded if too many or too few questions are asked.

Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000).—

The BRIEF is a parent- or caregiver-report questionnaire that assesses executive function and self-regulation skills in children and adolescents. Eight subscales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Planning/Organization, Organization of Materials, Monitor) comprise two composite scales (Behavioral Regulation Index, Metacognition Index) and an overall Global Executive Composite. The Behavioral Regulation Index (i.e., Inhibit, Shift, Emotional Control) assesses the individual's ability to maintain regulatory control of one's emotional responses and behavior. The Metacognition Index (i.e., Initiate, Working Memory, Planning/Organization, Organization of Materials, Monitor) assesses various aspects of executive function abilities related to cognition, including ability to initiate activity, problem solve, plan and organize, sustain working memory, organize materials, and evaluate success and failure. Responses on the BRIEF result in T-scores ($M = 50$; $SD = 10$), corrected for age and sex, with lower scores indicating better executive function and self-regulation skills. Clinical significance is indicated by T-scores greater than 65 on the BRIEF (Gioia et al., 2000). T-scores for the eight subscales were included in analyses.

Statistical Analyses

SPSS statistical software v.24 was used for all analyses. Demographic data were analyzed using either Pearson's chi-square (categorical data) or univariate analysis of variance (ANOVA; continuous data) techniques. Participants with missing data were excluded from the corresponding analyses. Data were assessed for outliers by group using boxplot technique and outliers more than 3 standard deviations from the mean were removed from analyses.

To determine the association between oppositional/conduct behaviors and alcohol exposure with direct and indirect measures of executive function, two separate multivariate analysis of covariance (MANCOVA) were used for neuropsychological data (D-KEFS) and parent-report data (BRIEF), respectively. Demographic variables were evaluated as covariates for each analysis and demographic variables were included in subsequent analyses when appropriate. First, for each analysis (neuropsychology data, D-KEFS; parent-report data, BRIEF) overall group differences were investigated and significant differences were followed up using univariate ANOVAs and pairwise comparisons. Second, to assess the relation between oppositional/conduct behaviors and executive function in alcohol-exposed children above and beyond ADHD, follow-up MANCOVAs were separately conducted within the AE groups for both the neuropsychological data and parent-report data.

Evaluation of Covariates

Covariates were assessed separately for analysis of direct (D-KEFS) and indirect (BRIEF) EF measures. Age and sex were investigated as potential covariates due to their theoretical relationship with executive function ability. Interaction terms between covariates (age, sex) and Group (AE+, AE-, CON) were created to assess homogeneity of regression assumptions for univariate analysis of covariance (ANCOVA) analyses. An alpha level of $p < .05$ was used to determine appropriateness as a covariate. For neuropsychology analyses, results showed no significant interactions between Group and sex ($ps > .070$) or Group and age ($ps > .070$) on the dependent variables (D-KEFS subtests). Age ($ps < .005$), but not sex ($ps = .147$), had a significant relationship with a majority of the dependent variables (i.e., 5 of 6 variables - all but Trail Making Number Sequencing). For parent-report analyses, results showed no significant relationships between Group and sex ($ps > .219$) or Group and age ($ps > .192$) on the dependent variables (BRIEF subscales). Site, race, and ethnicity were also investigated as potential covariates. For neuropsychology analyses, there were no significant relationships between the dependent variables (D-KEFS) and race ($ps > .138$) or ethnicity ($ps > .350$), although there were significant relationships between the dependent variables and site ($ps < .028$). Site also showed significant interactions with Group ($ps < .003$), and therefore was not an appropriate covariate. Instead, site differences are discussed separately, below. For parent-report analyses, results showed no significant relationships between the dependent variables (BRIEF) and race ($ps > .252$) or ethnicity ($ps > .101$). Results showed significant relationships between the dependent variables and site ($ps < .027$); however, site again showed significant interactions with Group ($ps < .007$) and as such was not an appropriate covariate. Therefore, age was included as a covariate in neuropsychology analyses, and no covariates were included in subsequent parent-report analyses.

Results

Demographic Data

Groups were matched on all demographic variables except age ($p = .033$), GCA ($p < .001$), and site ($p = .001$). Specifically, the AE+ ($M = 12.8$, $SD = 2.06$) and AE- ($M = 12.9$, $SD = 2.07$) groups were younger than the CON group ($M = 13.6$, $SD = 2.23$) and had significantly lower GCA scores (AE+: $M = 86.8$, $SD = 12.88$; AE-: $M = 90.2$, $SD = 12.68$) than the CON group ($M = 102.9$, $SD = 16.76$). In addition, certain sites recruited more participants for

specific groups (see Table 1). The AE groups were matched on all demographic variables except site ($p < .001$) and rate of ADHD diagnosis ($p < .001$). The AE+ group had a significantly higher proportion of subjects meeting criteria for ADHD ($n = 77, 75.5\%$) than the AE- group ($n = 18, 40.0\%$) and as above, recruitment by group varied by site (see Table 1). Demographic data are presented in Table 1.

Neuropsychology Results

Overall MANCOVA—Results from neuropsychological analyses are presented in Tables 2–3. Using an alpha level of .001 to evaluate homogeneity assumptions, Box’s M test of homogeneity of covariance ($p = .041$) and Levene’s homogeneity test ($ps > .010$) were not statistically significant. Using Wilk’s criterion (Λ) as the omnibus test statistic, the combined dependent variables resulted in a significant main effect for Group ($p = .001$). To probe the statistically significant multivariate effects, univariate ANOVAs were conducted on each individual dependent variable.

Overall, there was a significant main effect of Group on the majority of neuropsychological variables. Groups significantly differed ($ps < .049$) on Trail Making Number Sequencing, Trail Making Letter Sequencing, Trail Making Number-Letter Switching, and Twenty Questions Total Initial Abstraction (see Table 2). Follow-up analyses revealed the CON group performed significantly better than the AE+ and AE- groups, which did not differ from each other for all significant variables (see Table 3). There was no main effect of Group for Total Questions Asked ($p = .164$) and Total Weighted Achievement ($p = .050$) was trending towards significance.

Follow-up AE Group Analyses—As stated above, to evaluate our *a priori* hypotheses of whether the presence of ADHD significantly contributed to results, follow-up MANCOVAs with ADHD as a covariate were conducted between the AE groups only. Using an alpha level of .001 to evaluate homogeneity assumptions, Box’s M test of homogeneity of covariance ($p = .510$) and Levene’s homogeneity test ($ps > .195$) were not statistically significant. Using Wilk’s criterion (Λ) as the omnibus test statistic, the main effect for alcohol-exposed Group (AE+, AE-) was not significant ($p = .785$; see Figure 1). Thus, accounting for ADHD did not change the findings, as differences between AE+ and AE- were not statistically significant on any neuropsychological variables (see Table 3).

Parent-Report Results

Overall MANCOVA—Results from parent-report analyses are presented in Tables 4–5. Using an alpha level of .001 to evaluate homogeneity assumptions, Box’s M test of homogeneity of covariance ($p < .001$) and Levene’s homogeneity test ($ps < .001$) were statistically significant. However, MANCOVA is generally robust to these violations and as such these violations are likely not an issue. Using Wilk’s criterion (Λ) as the omnibus test statistic, the combined dependent variables resulted in a significant main effect for Group ($p < .001$). To probe the statistically significant multivariate effects, univariate ANOVAs were conducted on each individual dependent variable.

All BRIEF subscales showed a significant main effect for Group ($p < .001$; see Table 4). Follow-up analyses showed that CON was rated as significantly better than AE-, which was rated as significantly better than AE+ (see Table 5). Of note, higher scores on the BRIEF indicate greater dysfunction, and therefore better functioning is captured as lower scores.

Follow-up AE Group Analyses—To determine whether presence of ADHD significantly contributed to results, follow-up MANCOVAs with ADHD as a covariate were conducted between the AE groups only. Using an alpha level of .001 to evaluate homogeneity assumptions, Box's M test of homogeneity of covariance ($p = .009$) and Levene's homogeneity test ($p > .003$) were not statistically significant. Using Wilk's criterion (Λ) as the omnibus test statistic, the combined dependent variables resulted in a significant main effect ($p < .001$) for alcohol-exposed Group (AE+, AE-). To probe the statistically significant multivariate effects, univariate ANOVAs were conducted on each individual dependent variable. There was a statistically significant main effect ($p = .040$) for Group on four of the eight subscales (i.e., Inhibit, Shift, Emotional Control, Organization of Materials; see Table 4). On all four significant subscales, the AE- group was rated significantly better (lower BRIEF scores) than the AE+ group, which was within the clinically significant range for those scales (see Table 5). The main effect of Group was not significant ($p > .234$) for the other subscales (see Figure 2). Thus, accounting for the presence of ADHD did not change the significant group differences on four of the eight BRIEF scales (Inhibit, Shift, Emotional Control, Organization of Materials), with the AE- group continuing to be rated as significantly better (lower BRIEF scores) than the AE+ group.

Discussion

We investigated the association of heavy prenatal alcohol exposure and oppositional/conduct behaviors with executive function abilities both through direct neuropsychological testing and indirect parent report. Results indicate that for youth with prenatal alcohol exposure, the presence of oppositional/conduct behaviors was significantly associated with parent-reported executive function impairment to the point of clinical significance on four scales relevant for behavioral regulation, even when controlling for ADHD. Three of the four observed elevated scales (i.e., Inhibit, Shift, Emotional Control) make up the Behavioral Regulation Index of the BRIEF, indicating that parents of these children are reporting greater difficulty with behavioral regulation when oppositional/conduct behaviors co-occur with alcohol-exposure. Skills measured by these scales include inhibiting inappropriate responses, being able to shift attention, and regulating emotional responses in various situations (Gioia et al., 2000). Parents of youth with prenatal alcohol exposure are also reporting greater difficulty with Organization of Materials, though other scales of Metacognition are not similarly related to the presence of oppositionality, conduct-related behaviors, and alcohol-exposure. On neuropsychological measures of executive function, both alcohol-exposed groups were significantly impaired in relation to controls. In contrast to parent report, deficits on these direct measures of executive function were consistent across levels of oppositional/conduct behaviors and were not affected by the presence of ADHD. Thus, the current study extends the extant literature by showing that, unlike parent-report measures, cognitive measures are

not associated with greater impairment due to additional presence of oppositional/conduct behaviors in this population.

Previous studies have repeatedly shown that youth with heavy prenatal alcohol exposure demonstrate impaired executive function (Kodituwakku, 2007, Kodituwakku & Kodituwakku, 2014, Glass et al., 2013, Mattson et al., 2011, Mattson et al., 2013) as well as significant psychopathology (Burd et al., 2003, Disney et al., 2008, D'Onofrio et al., 2007, Fryer et al., 2007, Kodituwakku & Kodituwakku, 2014, Raldiris et al., 2014, Steinhausen and Spohr, 1998). Findings from the current study add to this burgeoning area of research and demonstrate that the combination of prenatal alcohol exposure and concurrent psychopathology (i.e., oppositional/conduct behaviors) is associated with poorer performance on some domains of executive function abilities as reported by parents and caregivers, though not as observed through direct neuropsychological measures. Furthermore, follow-up analyses showed that the presence of ADHD in addition to oppositional/conduct behaviors did not alter the relation between prenatal alcohol exposure and neuropsychological performance. These results are consistent with previous studies suggesting that concurrent psychopathology (e.g., ADHD) is not significantly associated with neuropsychological functioning above and beyond prenatal alcohol exposure (Glass et al., 2013).

While studies have examined the relation between oppositional/conduct behaviors and executive function among other populations, this is the first known study in youth with prenatal alcohol exposure. Our findings support previous studies of children with other developmental disorders demonstrating that, within the alcohol-exposed groups, the additional presence of ADHD did not appear to significantly alter performance on neuropsychological measures as compared to ODD/CD alone (Antonini et al., 2015, Ezpeleta and Granero, 2015). However, parents of alcohol-exposed youth continue to report greater behavioral impairment in those individuals with concurrent ADHD and oppositional/conduct behaviors (Barnett et al., 2009, Qian et al., 2010), specifically with regard to measures of behavioral regulation. Thus, even when controlling for presence of ADHD symptomatology, oppositional/conduct behaviors and prenatal alcohol exposure are associated with significantly impairing behavioral executive function deficits. Behavioral executive function deficits (i.e., those assessed by parent questionnaires) are often associated with adverse outcomes such as academic difficulties (Biederman et al., 2004), social impairments (Schonfeld et al., 2006), and involvement with the criminal justice system (Ogilvie et al., 2011). Thus, it is of particular importance to continue to refine understanding the relation between concurrent psychopathology and prenatal alcohol exposure on cognitive and behavioral functioning.

As shown previously (Nguyen et al., 2014), this study documents a difference between parent-report and direct measurements of executive function in youth with prenatal alcohol exposure. Both alcohol-exposed groups displayed impaired executive functioning on both direct and indirect measures. However, parents who reported oppositional/conduct behaviors (the AE+ group) in their children also reported greater executive function impairments than parents who reported fewer oppositional/conduct behaviors (the AE- group). This difference was not supported by direct assessment; the alcohol-exposed groups did not differ on the D-

KEFS subtests. The same results have been documented previously in studies of ADHD with and without oppositional/conduct behaviors (Barnett et al., 2009, Qian et al., 2010). It is likely that parents of youth with prenatal alcohol exposure experience and report greater distress than parents of youth in the control group. However, differential results between AE+ and AE- (i.e., AE+ elevated on 4 of 8 BRIEF scales as compared to AE- after accounting for ADHD) suggests that the observed differences are not fully attributable to elevated stress in parents of alcohol-exposed children and rather are related to the additional impact of other externalizing behaviors. Furthermore, all BRIEF reports were valid based on measure validity indicators (Gioia et al., 2000), suggesting adequate responding from parents and caregivers. It is possible this discrepancy is a result of study methodology as parents reported on oppositional and conduct behaviors (i.e., C-DISC-4.0) as well as behavioral executive function (i.e., BRIEF) while neuropsychological measures assessed the child's abilities directly. Future studies should include additional sources of information (e.g., teacher-report, self-report) to investigate factors driving this discrepancy between parent-report and direct measurement of executive function abilities among youth with heavy prenatal alcohol exposure.

Overall, these findings suggest that alcohol-exposed individuals with co-occurring oppositional/conduct behaviors experience significant impairment in both cognitive and behavioral executive function abilities. Importantly, parents of youth with prenatal alcohol exposure and oppositional/conduct behaviors report greater behavioral impairment than parents of youth with prenatal alcohol exposure alone. In fact, parents of youth with prenatal alcohol exposure alone did not report clinically significant behavioral executive function (i.e., $T > 65$). As such, interventions that improve aspects of behavioral executive function (Diamond & Lee, 2011) in combination with interventions targeted at cognitive abilities (e.g., computer games to improve inhibitory control) may be more effective than either modality alone to help these skills generalize to everyday functioning for youth with both alcohol exposure and oppositional/conduct behaviors. Parental education regarding appropriate structure and accommodations for executive function difficulties in youth with prenatal alcohol exposure will also likely provide support to reduce further stress and frustration. Further, findings from the current study suggest that interventions targeted at organizational skills may likewise be beneficial in alleviating functional deficits associated with both prenatal alcohol exposure and oppositional/conduct behaviors.

Limitations and Future Directions

Several limitations of the current study should be noted in the consideration of these findings. Concerns may include maternal drug use or smoking during pregnancy as these substances have been shown to result in externalizing behaviors among offspring (Bada et al., 2011, Cornelius et al., 2011, Holz et al., 2014, Ruckinger et al., 2010). The current study is retrospective in nature and unfortunately, we do not have specific, verified, information regarding maternal drug use during pregnancy. Even though alcohol is considered to be one of the most impactful teratogens above and beyond other substances, additional confounds should be noted as limitations within our sample. In addition, as our study is cross-sectional in nature, we are strictly reporting associations between observed variables and as such cannot determine causality. Due to our limited sample size and non-normally distributed

data (BRIEF), we were unable to employ other statistical methodology (e.g., structural equation modeling) that could explore directionality and relationships between variables. Future studies should aim to examine whether directionality exists among these variables.

We were also limited in options for collateral information (i.e., parent or caregiver). As such, overlap in reporting may exist in using the BRIEF and C-DISC-4.0. While our findings suggest some discrimination as not all scales were elevated on the BRIEF, we acknowledge the need for additional direct report. Unfortunately, we did not have other sources of information (e.g., teacher report) for the current study and future studies should consider inclusion of additional sources of information. Along those lines, we did not have information relevant to parental stress burden (e.g., socioeconomic status, psychopathology) and future studies should consider examining such factors. We were also limited in the cognitive measures available based on CIFASD study design. Future studies should aim to expand upon measures studied here including measures of inhibitory control.

Environmental factors may also have played a role in these results. As indicated above, research site was a significant factor in some results. Although not included in the main analyses, exploratory analyses indicated that site may have resulted in modest differences on both neuropsychological and parent report measures. However, these site differences were small in magnitude, present only on isolated measures, and not clinically significant (all scores were within the average range). An additional limitation to consider is the association of foster care or adoption with increased rates of oppositional/conduct behaviors (Latimer et al., 2012). Increased rates of foster care and adoption are evident among youth with prenatal alcohol exposure and a majority of individuals with FASD do not reside with their biological parents. Inclusion of a foster care or adoption comparison group may help elucidate the contribution of such factors to executive function and behavioral problems among youth with prenatal alcohol exposure. Along those lines, we did not specifically recruit an ODD/CD comparison group and inclusion of comparison groups with additional or different psychopathology would help further our knowledge of the specificity of the findings reported herein.

Some have suggested that executive dysfunction subtypes may exist among children with ADHD, including children with primarily poor inhibitory control, children with primarily poor set-shifting or speed, and those with intact performance (Roberts et al., 2017). Although the heterogeneous nature of FASD suggests that multiple profiles may exist, it has not yet been explicitly tested. Additionally, executive function impairments have been shown to significantly predict psychopathology in other neurodevelopmental disorders (e.g., autism spectrum disorders, ADHD; Lawson et al., 2015). Understanding whether this same predictive relationship is evident among youth with prenatal alcohol exposure may help elucidate the impact of cognitive deficits on long-term outcomes among these individuals.

Conclusions

Youth with heavy prenatal alcohol exposure exhibit executive function deficits and high rates of psychopathology. Overall, our findings show that the presence of oppositional/conduct behaviors in youth with heavy prenatal alcohol exposure is associated with deficits in behavioral regulation, though neuropsychological performance on executive function tasks is

not affected over the effects of prenatal alcohol exposure. In the cognitive domain, prenatal alcohol exposure affects executive functioning above and beyond oppositional/conduct behaviors or ADHD, while the combination of oppositional/conduct behaviors and prenatal alcohol exposure is associated with significantly worse performance on parent-report of behavioral functioning even after accounting for ADHD symptomatology. Interventions targeted at behavioral executive function in addition to cognitive functioning may be most beneficial in improving everyday functioning, including academic and social settings. Future research investigating potential executive dysfunction subtypes among youth with histories of heavy prenatal alcohol exposure will aid in further clarifying the neurobehavioral profile, or profiles, of FASD.

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Objective Executive Function

Figure 1.

Performance on D-KEFS subtests for subjects in three study groups: typically developing controls (CON), alcohol-exposed youth without oppositional/conduct behaviors (AE-), and alcohol-exposed youth with oppositional/conduct behaviors (AE+). *Note:* CON performed significantly better on 4 of 6 subtests (Trail Making [TM] Number, TM Letter Sequencing, TM Number-Letter Switching, Twenty Questions [TQ] Total Initial Abstraction) than AE+ and AE-, as denoted with asterisks, which did not differ. Groups did not differ on TQ Total Questions Asked or TQ Total Weighted Achievement (WA). AE+ and AE- again did not differ when accounting for ADHD.

Figure 2.

Performance on BRIEF subscales for subjects in three study groups: typically developing controls (CON), alcohol-exposed youth without oppositional/conduct behaviors (AE-), and alcohol-exposed youth with oppositional/conduct behaviors (AE+). Note: CON was rated significantly better than AE-, which was rated significantly better than AE+ on all subscales. AE- was rated significantly better than AE+ on 4 of 8 subscales (Inhibit, Shift, Emotional Control, Organization of Materials) when accounting for ADHD as denoted with asterisks. Dotted line indicates cutoff for clinical significance ($T > 65$).

Table 1.

Demographic information by Group.

Demographic Variable	AE+ (n=102)	AE- (n=45)	CON (n=120)
Sex [<i>n</i> (% Female)]	49 (48.0)	20 (44.4)	55 (45.8)
Age [<i>Mean</i> (SD)] [*]	12.8 (2.06)	12.9 (2.27)	13.6 (2.23)
Race [<i>n</i> (% White)]	51 (50.0)	24 (53.3)	60 (50.0)
Ethnicity [<i>n</i> (% Hispanic)]	22 (21.6)	10 (22.2)	24 (20.0)
Handedness [<i>n</i> (% Right)]	90 (88.2)	45 (100.0)	109 (90.8)
GCA [<i>Mean</i> (SD)] [*]	86.8 (12.88)	90.2 (12.68)	102.9 (16.76)
Research Diagnosis			
ADHD [<i>n</i> (%)] [*]	77 (75.5)	18 (40.0)	0 (0.0)
FAS [<i>n</i> (%)]	12 (11.8)	4 (8.9)	0 (0.0)
CIFASD Site [<i>n</i> (%)] [*]			
Atlanta	13 (12.7)	20 (44.4)	41 (34.2)
Los Angeles	16 (15.7)	6 (13.3)	22 (18.3)
Minnesota	36 (35.3)	8 (17.8)	23 (19.2)
San Diego	37 (36.3)	11 (24.4)	34 (28.3)

Note:

*
p < .05 level,

ADHD = attention-deficit/hyperactivity disorder, FAS = fetal alcohol syndrome. General Conceptual Ability (GCA), an estimate of general intellectual ability, was measured using the Differential Ability Scales – Second Edition (DAS-II). Groups included alcohol-exposed with oppositional/conduct behaviors (AE+), alcohol-exposed without oppositional/conduct behaviors (AE-), and typically developing controls (CON). The AE+ and AE- groups were younger than the CON and had lower GCA scores than the CON group. The AE+ group had a higher proportion of subjects meeting criteria for ADHD than the AE- group. Recruitment varied by site.

Table 2.

MANCOVA results for neuropsychology analyses.

D-KEFS Test	Overall			AE+ vs. AE- Controlling for ADHD		
	Group [F (df)]	<i>p</i>	Partial η^2	Group [F (df)]	<i>p</i>	Partial η^2
Omnibus	2.872* (12, 512)	.001	.063	0.530 (1, 146)	.785	.023
TM Number Sequencing	11.248** (2, 265)	<.001	.079	--	--	--
TM Letter Sequencing	7.128** (2, 265)	.001	.052	--	--	--
TM Number-Letter Switching	11.568** (2, 265)	<.001	.081	--	--	--
TQ Total Initial Abstraction	3.044* (2, 265)	.049	.023	--	--	--
TQ Total Questions Asked	1.820 (2, 265)	.164	.014	--	--	--
TQ Total Weighted Achievement	3.026 (2, 265)	.050	.023	--	--	--

Note:

* significant at $p < .05$ level,** significant at $p < .001$ level,

df = degrees of freedom. Scaled scores from the Trail Making (TM) and Twenty Questions (TQ) Tests from the Delis-Kaplan Executive Function System (D-KEFS) were included in analyses. Group included typically developing controls (CON), alcohol-exposed youth without oppositional/conduct behaviors (AE-), and alcohol-exposed youth with oppositional/conduct behaviors (AE+). Overall analyses examined differences between the three groups (CON, AE+, AE-). Differences between the AE groups (AE+ and AE-) were examined controlling for presence of ADHD.

Table 3.

Follow-up results for neuropsychology analyses.

D-KEFS Test	Means and MANCOVA Results				Follow-up
	CON	AE-	AE+	Pairwise Comparisons*	AE+ vs. AE- Controlling for ADHD
TM Number Sequencing	10.49	8.78	9.33	CON > AE+, AE-	NS
TM Letter Sequencing	9.92	7.73	8.14	CON > AE+, AE-	NS
TM Number-Letter Switching	9.33	7.02	7.01	CON > AE+, AE-	NS
TQ Total Questions Asked	9.68	7.82	8.85	CON > AE+, AE-	NS
TQ Initial Abstraction	9.54	8.09	8.46	NS	NS
TQ Total Weighted Achievement	9.73	7.58	8.74	NS	NS

Note:

* significant at $p < .05$ level,

NS = non-significant. Scaled scores from the Trail Making (TM) and Twenty Questions (TQ) Tests from the Delis-Kaplan Executive Function System (D-KEFS) were included in analyses. Group included typically developing controls (CON), alcohol-exposed youth without oppositional/conduct behaviors (AE-), and alcohol-exposed youth with oppositional/conduct behaviors (AE+). Overall analyses examined differences between the three groups (CON, AE+, AE-). Differences between the AE groups (AE+ and AE-) were examined controlling for presence of ADHD.

Table 4.

MANCOVA results for parent-report analyses

BRIEF Subscale	Overall			AE+ vs. AE- Controlling for ADHD		
	Group [F (df)]	<i>p</i>	Partial η^2	Group [F (df)]	<i>p</i>	Partial η^2
Omnibus	30.836** (16, 510)	<.001	.492	5.562** (8, 135)	<.001	.248
Inhibit	204.436** (2, 265)	<.001	.609	32.787** (1,146)	<.001	.188
Shift	129.423** (2, 265)	<.001	.497	4.289* (1,146)	.040	.029
Emotional Control	148.986** (2, 265)	<.001	.532	15.170** (1,146)	<.001	.097
Initiate	162.862** (2, 265)	<.001	.554	0.240 (1, 146)	.625	.002
Working Memory	188.332** (2, 265)	<.001	.590	0.914 (1, 146)	.341	.006
Planning/Organization	190.531** (2, 265)	<.001	.593	0.340 (1, 146)	.561	.002
Organization of Materials	92.632** (2, 265)	<.001	.414	4.520* (1,146)	.035	.031
Monitor	167.158** (2, 265)	<.001	.574	1.429 (1, 146)	.234	.010

Note:

*
significant at $p < .05$ level,**
significant at $p < .001$ level,

df = degrees of freedom. T-scores from all subscales of the Behavior Rating Inventory of Executive Function (BRIEF) were included in analyses. Group included typically developing controls (CON), alcohol-exposed youth without oppositional/conduct behaviors (AE-), and alcohol-exposed youth with oppositional/conduct behaviors (AE+). Overall analyses examined differences between the three groups (CON, AE+, AE-). Differences between the AE groups (AE+ and AE-) were examined controlling for presence of ADHD.

Table 5.

Follow-up results for parent-report analyses.

BRIEF Subscale	Means and MANCOVA Results				Follow-up
	CON	AE-	AE+	Pairwise Comparisons *	AE+ vs. AE- Controlling for ADHD
Inhibit	44.75	56.18	73.68	CON < AE- < AE+	AE- < AE+
Shift	44.60	59.76	68.41	CON < AE- < AE+	AE- < AE+
Emotional Control	43.33	54.93	66.67	CON < AE- < AE+	AE- < AE+
Initiate	44.25	60.89	65.96	CON < AE- < AE+	NS
Working Memory	45.72	64.76	71.62	CON < AE- < AE+	NS
Planning/Organization	45.02	62.98	69.56	CON < AE- < AE+	NS
Organization of Materials	45.34	55.29	61.83	CON < AE- < AE+	AE- < AE+
Monitor	42.26	60.07	67.74	CON < AE- < AE+	NS

Note:

* significant at $p < .05$ level,

NS = not significant. T-scores from all subscales of the Behavior Rating Inventory of Executive Function (BRIEF) were included in analyses. Group included typically developing controls (CON), alcohol-exposed youth without oppositional/conduct behaviors (AE-), and alcohol-exposed youth with oppositional/conduct behaviors (AE+). Of note, clinical significance on the BRIEF is defined at T = 65 and higher scores indicate greater impairment. Overall analyses examined differences between the three groups (CON, AE+, AE-). Differences between the AE groups (AE+ and AE-) were examined controlling for presence of ADHD.