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Further Development of a Neurobehavioral Profile of Fetal Alcohol Spectrum Disorders

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Abstract

Background—Heavy prenatal alcohol exposure (AE) results in a broad array of neurobehavioral deficits. Recent research has focused on identification of a neurobehavioral profile or profiles that will improve identification of children affected by AE. The current study aimed to build on our preliminary neurobehavioral profile in order to improve classification accuracy and test the specificity of the resulting profile in an alternate clinical group.

Methods—A standardized neuropsychological test battery was administered to three groups of children: subjects with AE (n = 209), typically developing controls (CON, n = 185), and subjects with attention-deficit/hyperactivity disorder (ADHD, n = 74). We assessed a large sample from six sites in the U.S. and South Africa, using standardized methodology. Data were analyzed using three latent profile analyses (LPA) including: (1) subjects with FAS and controls, (2) subjects with

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

AE without FAS and controls, (3) subjects with AE (with or without FAS) and subjects with ADHD.

Results—Classification accuracy was moderate but significant across the three analyses. In analysis 1, overall classification accuracy was 76.1% (77.2% FAS, 75.7% CON). In the second analysis, overall classification accuracy was 71.5% (70.1% AE/Non-FAS, 72.4% CON). In the third analysis, overall classification accuracy was 73.9% (59.8% AE, 75.7% ADHD). Subjects that were misclassified were examined for systematic differences from those that were correctly classified.

Conclusion—The results of this study indicate that the neuropsychological effects of AE are clinically meaningful and can be used to accurately distinguish alcohol-affected children from both typically developing children and children with ADHD. Further, in combination with other recent studies, these data suggest that approximately 70% of children with heavy prenatal alcohol exposure are neurobehaviorally affected while the remaining 30% are spared these often-devastating consequences, at least those in the domains under study. Refining the neurobehavioral profile will allow improved identification and treatment development for children affected by prenatal alcohol exposure.

Keywords

Fetal Alcohol Syndrome (FAS); Prenatal Alcohol Exposure; Neurobehavioral Profile; Attention-Deficit/Hyperactivity Disorder (ADHD); Latent Profile Analysis (LPA)

Introduction

Prenatal alcohol exposure (AE) is a leading preventable cause of birth defects, developmental disorders, and mental retardation (American Academy of Pediatrics Committee on Substance Abuse and Committee on Children With Disabilities, 2000). A subset of children with histories of heavy prenatal alcohol exposure meet the diagnostic criteria for fetal alcohol syndrome (FAS), which consist of craniofacial dysmorphology, growth deficiency, and evidence of central nervous system involvement (Hoyme et al., 2005, Stratton et al., 1996, Bertrand et al., 2005, Jones and Smith, 1973). While the diagnostic criteria for FAS serve as an avenue for identification of some children with AE, the majority of children affected by such exposure do not exhibit enough of the characteristic physical features to receive an FAS diagnosis (Bertrand et al., 2005, Sampson et al., 1997). Even in the absence of FAS, however, they exhibit similar neurobehavioral impairments as children with FAS (e.g., Mattson et al., 1997, Mattson and Riley, 1998, Mattson et al., 1998, Mattson et al., 2011).

Fetal alcohol spectrum disorders (FASD) encompass a wider range of outcomes and include affected children with and without FAS. The prevalence of FAS is 2–7 per 1000 live births (0.2–0.7%) in the U.S., and recent estimates suggest that FASD occurs at a rate of 2–5 per 100 younger school children (2–5%) in the U.S. and some Western European countries (May et al., 2009). In addition to the lack of definitive markers of AE, other factors limit the ability to identify alcohol-affected individuals (Mattson and Riley, 2011). Overlap with other clinical conditions, variability in exposure histories, and degree of impairment may also affect accurate clinical identification. In an effort to improve identification of alcohol-affected children across the spectrum of effects, research has focused increasingly on development of a profile based on impaired and spared cognitive abilities in children with AE. Such a neurobehavioral profile of AE would greatly assist the development of more precise diagnostic criteria for identification and improve treatment by more specifically defining the nature of the neurobehavioral deficits related to AE (Mattson and Riley, 2011).

The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) is a multi-site, interdisciplinary project aimed at characterizing structural and functional deficits in FASD to enhance understanding of both dysmorphology and the neurobehavioral phenotype (Mattson et al., 2010a). A previous study from the CIFASD program used latent profile analysis (LPA) to classify subjects with AE and controls. Using 22 neuropsychological variables with medium to large effect sizes, a 2-class model best fit the data with an overall success rate of 92% accuracy in distinguishing FAS from non-exposed controls; 87.8% of FAS cases and 95.7% of controls were correctly classified. Similar results were found when the profile was tested using AE subjects without FAS and controls: overall classification accuracy was 84.7%; 68.4% of alcohol-exposed and 95% of controls were correctly classified. In these analyses, executive functioning and spatial processing measures were most sensitive to prenatal alcohol exposure (Mattson et al., 2010b). The specificity of the profile was not tested. The current study aimed to build upon this preliminary neurobehavioral profile to (1) improve our classification accuracy, particularly for alcohol-exposed subjects without FAS and (2) test the specificity of the resulting profile in an alternate clinical group. Using a standardized neuropsychological test battery, we examined children with AE, typically developing controls, and non-exposed children with attention-deficit/hyperactivity disorder (ADHD). A large sample of subjects was assessed at multiple sites using standardized methodology.

Materials and Methods

General Methods

Children between the ages 8–17 years were recruited for an ongoing multisite research study conducted by CIFASD. Details about the CIFASD clinical projects have been described elsewhere (Mattson et al., 2010a). Children included in this study comprised 3 groups: those with heavy prenatal alcohol exposure (the AE group), non-exposed children with a diagnosis of ADHD (the ADHD group), and typically developing non-exposed control children (the CON group).

Children included in the AE group were recruited retrospectively and had known histories of heavy prenatal alcohol exposure, defined as maternal consumption of more than 4 alcoholic drinks at least once per week or 14 drinks per week throughout the pregnancy. Prenatal exposure to alcohol was confirmed through medical history, birth records, social services records, and maternal report and questionnaires, when available. FAS diagnoses were determined via a comprehensive clinical exam by a member of the CIFASD Dysmorphology Core, using a standardized assessment of physical, craniofacial, and growth anomalies. For the purposes of this research project, children in the AE group were categorized as having FAS if they met the following criteria: structural abnormality (i.e., two or more of the following facial features: short palpebral fissure length, smooth philtrum, thin vermillion border) and either growth deficiency (height or weight ≤ 10%) or microcephaly (occipital-frontal circumference ≤ 10%). Details of the CIFASD Dysmorphology Core diagnostic criteria have been published elsewhere (Mattson et al., 2010a, Jones et al., 2010, Jones et al., 2006).

As part of this project, which represents the second phase of data collection for CIFASD (CIFASD II), neurobehavioral testing took place at multiple research centers across the United States and South Africa, including (1) the Center for Behavioral Teratology at San Diego State University, (2) The Fetal Alcohol and Drug Exposure Clinic at Emory University, (3) Center on Alcoholism, Substance Abuse and Addictions at the University of New Mexico, (4) seven different communities throughout North Dakota, South Dakota, and Montana (Northern Plains), (5) the Fetal Alcohol and Related Disorders Clinic at the University of California, Los Angeles, and (6) the University of Cape Town, South Africa.

Recruitment for the AE group differed by site location (for details see (Mattson et al., 2010a)). Subjects were recruited through various modalities from individual sites for on-going research or specifically for CIFASD. The varied testing sites ensure a large heterogeneous study population that is not biased by location or specific site characteristics. Data for this analysis were collected between 2008 and 2011.

Subjects in the ADHD and CON groups were screened for prenatal alcohol exposure and were only included if exposure levels were less than minimal exposure, defined as no more than one drink per week on average and never more than 2 drinks on a single occasion throughout gestation. Control and ADHD subjects were recruited to match the AE subjects recruited at that site. Exclusion criteria for all groups were: history of significant head injury or loss of consciousness > 30 minutes, non-fluent speaker of English (U.S. sites) or Afrikaans (South African site), inability to participate due to psychiatric or physical disability, evidence of other known causes of mental deficiency (e.g., congenital hypothyroidism, or genetic disorders), adoption from abroad after the age of 5 years old or less than 2 years before assessment, or any missing neuropsychological test data (Mattson et al., 2010a).

A standardized neuropsychological battery was administered in a single day to each child by a trained examiner blind to subject group. The CIFASD II test battery focuses more heavily on the domain of executive function than our previous test battery, (Mattson et al., 2010a) although it does include a range of cognitive domains, including general intellectual function, attention, and memory. Parent interviews and questionnaires were administered to primary caregivers. Caregivers completed the clinician-assisted National Institute of Mental Health Computerized Diagnostic Interview Schedule for Children IV (C-DISC-4.0; Shaffer et al., 2000) to determine ADHD diagnosis, along with any comorbid psychopathology. The C-DISC-4.0 provides diagnostic information based on the Diagnostic and Statistical Manual of the American Psychiatric Association (*DSM-IV*; American Psychiatric Association, 2000). Informed assent and consent were obtained from all subjects and their parents prior to testing. Subject incentive was provided to parents and children. The Institutional Review Board (IRB) at San Diego State University and other CIFASD sites approved this study.

Subjects

Subjects ($N = 468$) were between 8 and 17 years of age ($M = 12.25$, $SD = 2.65$). The AE group ($n = 209$) comprised children with confirmed histories of heavy prenatal alcohol exposure as described above. Standardized dysmorphology examinations were conducted according to CIFASD procedures (Mattson et al., 2010a, Jones et al., 2010, Jones et al., 2006) and dysmorphology data were available for 196 children in the alcohol-exposed group and of these, 79 (40.3%) met criteria for FAS. Similarly, children from 5 sites (all but the South African site) were screened for ADHD using the C-DISC-4.0 and 65 (60.2%) in the AE group met diagnostic criteria for ADHD. The CON group ($n = 185$) consisted of typically developing children who did not meet diagnostic criteria for FAS or ADHD, and had histories of little to no prenatal exposure to alcohol, as described above. Children were excluded from the CON group if they demonstrated clinical or subclinical symptoms of ADHD, as defined by the C-DISC-4.0. While the South African site did not recruit subjects with ADHD, control subjects were screened using a checklist based on *DSM-IV* criteria for ADHD and excluded if they exceeded the standard cutoff for possible ADHD. The ADHD group ($n = 74$) consisted of non-exposed children who met full *DSM-IV* diagnostic criteria for ADHD, based on the C-DISC-4.0. At each site, subjects were recruited from the local communities as described above and CON and ADHD subjects were recruited to match the AE subjects at that site.

Neuropsychological Measures

A standardized neuropsychological test battery was administered to all subjects. Tests were administered in English (U.S. sites) or Afrikaans (South African site). The tests included in this battery were: the Cambridge Neuropsychological Test Automated Battery (CANTAB: Delayed Matching to Sample, Intra-Extra Dimensional Shift, Choice Reaction Time, Simple Reaction Time, Spatial Working Memory subtests) (Cambridge Cognition, 2006) and the Delis-Kaplan Executive Function System (D-KEFS: Color-word Interference, Trail Making, 20 Questions, Tower, Verbal Fluency, Design Fluency subtests) (Delis et al., 2001). Full Scale IQ (FSIQ) scores were obtained using the Wechsler Intelligence Scale for Children – fourth edition (WISC-IV; Wechsler, 2004). Test results were administered and scored by the examiner according to published test manuals and rechecked by a second trained person. Scores were converted to standard scores or z-scores according to age norms when available and data were entered into a centralized database, which required double entry for verification of accuracy. Given the large number of variables available from this dataset, we selected a parsimonious set of summary variables from each measure. Variables were selected using clinical judgment and expertise of the authors to represent primary variables from each measure. Prior to analysis, correlations among variables were tested and those with strong correlations ($r > .6$) were excluded. As a result, variables from 2 measures (CANTAB Choice Reaction Time and D-KEFS Design Fluency) were excluded from further analysis. The resulting dataset included 11 variables, which are listed in Table 1.

Statistical Analysis

As in our previous study (Mattson et al., 2010b), latent profile analysis (LPA) was conducted to derive latent profiles that describe different categorical types of participants. LPA is a person-centered statistical approach that classifies individuals into groups based on their patterns of responses to sets of observed variables (Hagenaars and McCutcheon, 2002, McCutcheon, 1987, Lanza et al., 2003, Lanza et al., 2010, Roesch et al., 2010). The primary goal of LPA is to maximize the homogeneity within groups (i.e., individuals within a class/profile should look similar) and maximize the heterogeneity between groups (i.e., individuals between classes/profile groups should look different). These groups are represented by a categorical latent variable, as they are inferred from the response patterns on observed variables. LPA assumes a simple parametric model and uses the observed data to estimate parameter values for the model. This model-based approach is preferable to more subjective grouping techniques such as cluster analysis due to mathematical strengths, less subjectivity, and the ability to weight independent variables differentially and generate group probability predictions (Vermunt and Magidson, 2002). Model parameters are estimated using the maximum likelihood (ML) criterion. In the current study the 11 neuropsychological assessment variables (Table 1) were used as indicators (observed variables) to derive the latent profiles.

The determination of the *optimal* number of classes or profiles requires the specification and testing of multiple class solutions (1-class, 2-class, etc.). From these models, the designation of the “best-fitting” model is determined using a variety of statistical indicators. In the current study, model fit was determined using the Akaike Information Criteria (Akaike, 1974) and the sample size-adjusted Bayesian Information Criterion (Sclove, 1987), with lower values for these fit indicators indicating better model fit (Tofighi and Enders, 2008, Yang, 2006). In addition, the entropy index (the percentage of individuals in the sample that were correctly classified given the specific class model) was used because it indicates how well the profiles can be distinguished; this value is not meaningful in 1-class solutions. Entropy values greater than 80% are considered noteworthy (Ramaswamy et al., 1993). Once the number of profiles is determined, conditional response means (CRMs) are interpreted to substantively characterize those within each profile. CRMs indicate the mean

value for an observed variable within a profile. All models were estimated using MPlus (Muthén and Muthén, 2006). Three LPAs were conducted with the following *a priori* subject comparisons: (1) subjects with AE and a diagnosis of FAS and non-exposed controls, (2) subjects with AE without FAS and non-exposed controls, and (3) subjects with AE (with and without FAS), and non-exposed subjects with ADHD. The same neuropsychological variables were included in all analyses and 1-, 2-, and 3-class solutions were evaluated. With these analyses, we aimed to determine whether our neuropsychological data could distinguish alcohol-exposed subjects from controls and whether this profile was specific to the effects of heavy prenatal alcohol exposure compared to a clinical contrast group. Logistic regression analyses with classification tables were evaluated subsequent to the LPAs. The profiles were crossed with the target comparison groups (e.g., AE vs. CON) to evaluate how well the classes predicted group membership.

RESULTS

Demographics

Demographic data for the study groups are listed in Table 2. These data were analyzed using Fisher's exact test or Chi-square test for categorical data and ANOVA for continuous data. An alpha level of $p < .05$ was used to determine statistical significance. Alpha levels of $p = .05–.08$ were considered to be marginally significant. The AE/FAS group differed from the CON group on race, ethnicity, country of origin (U.S. vs. South Africa), and, as expected, on growth variables, microcephaly, measures of structural abnormality, presence of an ADHD diagnosis, and FSIQ. They were marginally different on handedness (Fisher's exact $p = .072$). They did not differ on sex or age. The AE/Non-FAS group differed from the CON group on race, growth variables, microcephaly, measures of structural abnormality, presence of an ADHD diagnosis, and FSIQ. They were marginally different on handedness (Fisher's exact $p = .050$). The two groups did not differ on sex, ethnicity, country of origin, or age. The combined AE group differed from the ADHD group on age, sex, race, ethnicity, country of origin, growth variables, microcephaly, measures of structural abnormality, presence of an ADHD diagnosis, and FSIQ. These two groups did not differ on handedness. Specific statistical results are listed in Table 2. Differences in basic demographic characteristics are likely related to site characteristics (e.g., the South African site is exclusively non-White and non-Hispanic).

Latent Profile Analysis

Analysis 1: Alcohol-Exposed (FAS) vs. Control—Descriptive group data for this analysis are included in Table 3 and in the supplemental table. For the first analysis, which included alcohol-exposed (AE/FAS) and CON groups, a 2-class solution fit better than a 1-class solution (AIC: 11910 vs. 12581; sBIC: 11923 vs. 12590; Entropy index for 2-class model = .89). For the 2-class solution, 106 participants were assigned to profile 1 (40% of the sample) and 158 participants were assigned to profile 2 (60% of the sample). As shown in Table 4, the CRMs indicate that individuals in profile 1 perform more poorly than individuals in profile 2 for each of the 11 observed variables characterizing the profiles. Effect sizes (Cohen's *d*) ranged from 0.55 to 2.38.

Logistic regression was then used to evaluate the association between the 2 latent profiles and a binary indicator variable representing the AE/FAS (coded 1) vs. the CON group (coded 0). The latent profile variable was significantly associated with group membership ($OR = 0.10$, $CI = .05$ to $.18$, $p < .001$), with significantly more individuals from the AE/FAS group in profile 1 and significantly more individuals from the CON group in profile 2. The profiles accounted for 76.1% accuracy of prediction in the two groups combined, with 77.2% accuracy in the AE/FAS group and 75.7% accuracy in the CON group.

Analysis 2: Alcohol-Exposed (without FAS) vs. Control—Descriptive group data for this analysis are included in Table 3 and in the supplemental table. For the second analysis, which included subjects in the AE/Non-FAS group and the CON group, a 2-class solution also fit better than a 1-class solution (AIC: 13595 vs. 14210; sBIC: 13614 vs. 14222; Entropy index for 2-class model = .84). For the resulting 2-class solution, 133 participants were assigned to profile 1 (44% of the sample) and 169 participants were assigned to profile 2 (56% of the sample). As shown in Table 5, the CRMs indicate that individuals in profile 1 perform more poorly than individuals in profile 2 for each of the 11 observed variables characterizing the profiles. Effect sizes (Cohen's *d*) ranged from 0.64 to 1.93.

Logistic regression was then used to evaluate the association between the 2 latent profiles and a binary variable representing the subjects that were from the AE/Non-FAS group (coded 1) vs. CON group (coded 0). The latent profile variable was significantly associated with group membership (*OR* = 0.16, *CI* = .10 to .27, $p < .001$), with significantly more AE/Non-FAS subjects in profile 1 and significantly more CON subjects in profile 2. The profiles accounted for 71.5% accuracy of prediction in the two groups combined, with 70.1% accuracy in the AE/Non-FAS group and 72.4% accuracy in the CON group.

Analysis 3: Alcohol-Exposed vs. ADHD—Descriptive group data for this analysis are included in Table 3 and in the supplemental table. For the third analysis, which included subjects with AE and non-exposed children with ADHD, a 2-class solution fit better than a 1-class solution (AIC: 13562 vs. 13979; sBIC: 13579 vs. 13990; Entropy index for 2-class model = .83). For the resulting 2-class solution, 143 participants were assigned to profile 1 (51% of the sample) and 140 participants were assigned to profile 2 (49% of the sample). As shown in Table 6, the CRMs indicate that individuals in profile 1 perform more poorly than individuals in profile 2 for each of the 11 observed variables characterizing the profiles. With the exception of one variable (CANTAB Simple Reaction Time), effect sizes (Cohen's d) ranged from 0.40 to 2.22.

Logistic regression was then used to evaluate the association between the 2 latent profiles and a binary variable representing the subjects with AE (coded 1) vs. ADHD (coded 0). The latent profile variable was significantly associated with group membership (*OR* = 0.22, *CI* = .12 to .39, $p < .001$), with significantly more AE subjects in profile 1 and significantly more ADHD subjects in profile 2. The profiles accounted for 73.9% accuracy of prediction in the two groups combined, with 59.8% accuracy in the AE group and 75.7% accuracy in the ADHD group.

Misclassified Subjects

Classification accuracy ranged from 60% to 76%. While these classification rates are statistically significant, both exposed and non-exposed subjects were misclassified. To determine if there were any systematic differences accounting for the misclassification, we compared subjects that were misclassified to those that were correctly classified for each analysis described above. Two continuous variables, age and FSIQ, were tested using ANOVA. The following categorical variables were tested by Fisher's exact test or chi-square: sex, handedness, country (U.S. vs. South Africa), race, ethnicity, growth deficiency (height or weight ≤ 10%), height ≤ 10%, weight (≤10%), microcephaly (OFC ≤ 10%), structural abnormality (two or more of the following facial features: short palpebral fissure length, smooth philtrum, thin vermillion border), short palpebral fissures, smooth philtrum, thin vermillion border, ADHD diagnosis. Presence or absence of physical features were analyzed individually as well as grouped into the structural abnormality and growth

deficiency variables. See Table 2 for descriptive data and definitions of the variables included.

Analysis 1: Alcohol-Exposed (FAS) vs. Control—There were 18 subjects with FAS that were misclassified as CON. In comparison to the FAS subjects that were correctly classified ($n = 61$), these subjects differed significantly ($p < .05$) on FSIQ (higher), country (more from U.S. than South Africa), and race (more White subjects). They were marginally different on microcephaly (less likely; Fisher's exact $p = .063$). They did not differ on age, sex, handedness, ethnicity, any measure of growth deficiency, any measure of structural abnormality, or presence of an ADHD diagnosis. On the neuropsychological measures, they differed (misclassified > correctly classified) significantly on all measures except the two CANTAB Intra-Extra Dimensional Shift measures (Stages completed, $p = .065$, Errors, $p = .116$).

There were 45 controls misclassified as FAS. In comparison to the controls that were correctly classified ($n = 140$), these subjects differed significantly on age (younger), FSIQ (lower), country (more from South Africa than U.S.), race (fewer White subjects), ethnicity (fewer Hispanic subjects), growth deficiency (more likely), and microcephaly (more likely). They were marginally different on weight (more likely to be $\leq 10^{th}$ percentile; Fisher's exact $p = .056$) and smooth philtrum (more likely; Fisher's exact $p = .069$). They were not different on sex, handedness, height, or structural abnormality, short palpebral fissures, or thin vermillion. They differed significantly on all of the neuropsychological variables (misclassified < correctly classified).

Analysis 2: Alcohol-Exposed (without FAS) vs. Control—There were 35 AE/Non-FAS subjects that were misclassified as CON. In comparison to the AE subjects that were correctly classified ($n = 82$), these subjects differed significantly on FSIQ (higher), country (fewer from South Africa than U.S.), race (more White subjects), ethnicity (more Hispanic subjects), growth deficiency (less likely), weight (less likely to be $\leq 10^{th}$ percentile), microcephaly (less likely), and thin vermillion (less likely). They did not differ on age, sex, handedness, ethnicity, height, structural abnormality, short palpebral fissures, smooth philtrum, or presence of an ADHD diagnosis. They differed significantly on all of the neuropsychological variables (misclassified > correctly classified).

There were 51 CON subjects misclassified as AE/Non-FAS. In comparison to the CON subjects that were correctly classified ($n = 134$), these subjects differed significantly on age (younger), FSIQ (lower), country (more from South Africa than U.S.), race (fewer White subjects), ethnicity (fewer Hispanic subjects), microcephaly (more likely), and smooth philtrum (more likely). They were marginally different on growth deficiency (more likely; Fisher's exact $p = .079$) and weight (more likely to be $\leq 10^{th}$ percentile; Fisher's exact $p = .062$). They were not different on sex, handedness, height, structural abnormality, short palpebral fissures, or thin vermillion. They differed significantly on all of the neuropsychological variables (misclassified < correctly classified).

Analysis 3: Alcohol-Exposed vs. ADHD—There were 84 subjects with AE misclassified as ADHD. In comparison to the AE subjects that were correctly classified ($n = 125$), these subjects differed significantly on FSIQ (higher), country (fewer from South Africa than U.S.), race (more White), ethnicity (more Hispanic), all measures of growth deficiency (less likely), microcephaly (less likely), structural abnormality (less likely), and thin vermillion (less likely). They were marginally different on handedness (fewer right handed; Fisher's exact $p = .075$), short palpebral fissures (less likely; Fisher's exact $p = .077$), and smooth philtrum (less likely; Fisher's exact $p = .078$). They did not differ on age,

sex, or presence of an ADHD diagnosis. They differed significantly on all of the neuropsychological variables (misclassified > correctly classified).

There were 18 subjects with ADHD misclassified as AE. In comparison to the ADHD subjects that were correctly classified ($n = 56$), these subjects differed significantly on FSIQ (lower). They were marginally different on handedness (more left-or mixed-handed; Fisher's exact $p = .055$). They did not differ on age, sex, ethnicity, race, any measure of growth deficiency, microcephaly, or any measure of structural abnormality. On the neuropsychological measures, they differed significantly (misclassified < correctly classified) on all measures except CANTAB Simple Reaction Time ($p = .934$) and D-KEFS Verbal Fluency Switching ($p = .134$).

Additional Covariates

Because race, ethnicity, and age were consistently related to misclassification of subjects, we conducted three hierarchical logistic regressions predicting the observed group. For each analysis, race (White vs. Non-White), ethnicity (Hispanic vs. Non-Hispanic), and age were entered on step 1 and the derived profile variable was entered on step 2. For the first analysis including the FAS and CON groups, race ($OR = .39$, $CI = .22 – .69$) and ethnicity ($OR = .11$, $CI = .01 – .81$) were both significantly associated with observed group. When the profile variable was entered, it was also significantly associated with observed group ($OR = .08$, $CI = .04 – .18$) and including the profile variable rendered race and ethnicity non-significant. In the second analysis including AE/Non-FAS and CON subjects, race ($OR = .39$, $CI = .24 – .65$) was significantly associated with observed group. When the profile variable was entered, it was also significantly associated with observed group ($OR = .14$, $CI = .08–.27$) and the entry of the profile variable rendered the covariate of race non-significant. For the third analysis, including AE and ADHD subjects, race ($OR = .17$, $CI = .09–.31$) and age ($OR = 1.18$, $CI = 1.05–1.33$) were significantly associated with observed group. When the profile variable was entered it was also significantly associated with observed group ($OR = .36$, $CI = .18–.71$). The two statistically significant covariates remained statistically significant on step 2. Thus, while race, ethnicity, and age are important covariates, their inclusion does not change the significance of the profile in predicting group membership.

Supplemental Analyses

Because of the role that country of origin (and intrinsically related factors) played in the misclassification of subjects and overall classification accuracies, the three analyses were repeated excluding the South African cohort. As in the main analyses, the analyses indicated that a 2-class solution fit better than a 1-class solution for the first two analyses (including (1) AE/FAS and CON and (2) AE/Non-FAS and CON). Follow up logistic regressions indicated overall classifications of 63% and 77%, respectively, both of which are statistically significant ($p < .01$). For the third analysis, including children with AE and ADHD, the 2-class solution did not fit the model better than a 1-class solution and no further analyses were conducted.

Discussion

In this study, we examined our ability to develop a profile of FASD based on neuropsychological variables. In comparison to our previous study (Mattson et al., 2010b), we used a larger dataset ($N = 468$) collected from five sites in the U.S. and one site in South Africa and included a clinical contrast group of non-exposed children with ADHD. Our aim was to improve our classification of AE children with and without FAS and to test the specificity of our profile. The addition of this clinical contrast group is critical in that it lends additional clinical significance and utility to our results. As in our previous study, our ability

to accurately classify subjects with AE was statistically significant. Our classification accuracy for FAS subjects was somewhat reduced from our previous study, while classification accuracy for the AE subjects without FAS was slightly improved. In the first study, we accurately classified 88% of FAS and 68% of AE/Non-FAS subjects. In the current study, these classification rates were 77% and 70%, respectively. There were several significant differences between the two studies that could account for these results, such as included sites and the variables chosen for analysis. In the first study (CIFASD I), just two sites were included: San Diego and Helsinki, Finland. In the current study (CIFASD II), data were collected from five U.S. sites and one South African site, which increased the heterogeneity of the sample. The increase in sample diversity related to changing sites likely increased the variability of neuropsychological test performance and may have lead to lower classification rates. In addition, a different strategy was used for selecting the neuropsychological variables for analysis. In the first study, we chose variables based on their ability to differentiate the AE from CON subjects in univariate analyses. In the current study, we used clinical judgment and chose the traditional variables from each measure. Although the effect sizes for these variables were mostly in the large range, the inclusion of additional or different variables may have improved our classification accuracy. In the previous study, we included 22 variables, while there were only 11 included in the current study. We selected a smaller number of variables in order to achieve a more parsimonious neuropsychological variable list, which would be more feasible for a clinical setting. Even given the increased heterogeneity and reduced number of variables, the classification accuracy of both FAS and non-FAS subjects with AE was highly statistically significant.

In the current study, we also included an ADHD clinical contrast group to test whether our neurobehavioral profile was specific to the effects of AE. This comparison is critically important given the high rate of ADHD in the AE population and the difficulty in clinically differentiating non-exposed children with ADHD from children with AE, especially in the absence of physical dysmorphology (Fryer et al., 2007). In the third set of analyses, we were able to accurately classify 59.8% of the AE subjects and 75.7% of the ADHD subjects, which was statistically significant. Thus, the neurobehavioral measures that distinguish AE subjects from controls can also be used to distinguish AE subjects from those with ADHD. While statistically significant, however, the relatively low classification rate for the AE subjects means that this profile is less desirable from a clinical perspective. Interestingly, the ability to classify subjects with ADHD was higher than the ability to accurately classify the AE subjects suggesting that this profile has stronger specificity than sensitivity in relation to AE. In addition, when analyses were conducted without subjects from the South African cohort, the results were no longer significant and did not support a unique profile of AE. Changes in sample size, and thus statistical power may have impacted this supplemental analysis. Regardless, future research should investigate whether a different profile exists for the comparison between AE and ADHD or whether the combination of this profile and other measures that improve sensitivity can improve classification accuracy for alcohol-affected subjects.

These results support and extend previous analyses demonstrating differences between AE and ADHD on neuropsychological variables (e.g., Vaurio et al., 2008, Crocker et al., 2009, Greenbaum et al., 2009, Crocker et al., 2011, Jacobson et al., 2011a, Kooistra et al., 2011). Specifically, in the third analysis comparing AE and ADHD, the variables with the largest effect sizes were measures of executive function, spatial working memory, and delayed matching to sample, which further substantiates previously documented group differences in executive function (Vaurio et al., 2008). However, there were some measures that proved to be less valuable in distinguishing the groups, namely CANTAB Intra-Extra Dimensional Shift, CANTAB Simple Reaction time, and D-KEFS Verbal Fluency Switching. Additional study is needed to more precisely define a neurobehavioral profile that distinguishes AE and

ADHD. This is especially important given that 50–80% of individuals with AE are estimated to also have ADHD (Fryer et al., 2007, Streissguth et al., 1999, Streissguth et al., 2004, Bhatara et al., 2006, Jacobson et al., 2011b).

While the classification rates for all three analyses were statistically significant, there were a reasonable number of subjects that were misclassified. Examination of the differences between the misclassified subjects and those who were correctly classified yielded useful clinical information. Knowledge about which subjects are more likely to be misclassified may be just as important as knowing how to classify subjects with AE. For example, our data show that in this sample, controls who were younger, with lower IQ scores, and/or from South Africa were more likely to be misclassified as AE. In contrast, AE subjects from the U.S., with higher IQ, were more likely than other AE subjects to be misclassified as controls. It is difficult to disentangle the factors that led to misclassification as some of the factors may be related to country of origin. Children in this study from South Africa are exclusively non-White and non-Hispanic. They also come from more vulnerable, less stimulating environments (Adnams et al., 2007) and are physically smaller (May et al., 2007) than subjects from the U.S. Future studies with different samples will help clarify these results. Supplemental analyses without the South African cohort yielded similar findings, although the classification accuracies, while statistically significant, were lower for the first analysis (FAS and CON) and higher for the second analysis (AE/Non-FAS and CON).

When considered together with our initial study (Mattson et al., 2010b) the data presented herein indicate that approximately 70% of children with heavy prenatal alcohol exposure without FAS are neurobehaviorally affected, even in the absence of FAS. These children would likely be classified as having alcohol-related neurodevelopmental disorder, which falls under the umbrella of FASD (Hoyme et al., 2005, Stratton et al., 1996, Bertrand et al., 2005). Conversely, 30% of this population appears to be spared neuropsychological and behavioral consequences. Examination of the test scores of the misclassified subjects in analysis 2 confirms this suggestion: for all 11 variables as well as IQ, the average score was within the average range. These findings are similar to two other recent studies. In the first, 78% of alcohol-exposed children without ADHD were distinguished from controls using 4 items from the Sluggish Cognitive Tempo Scale (Graham et al., 2011). In the second study, the combination of attention skills and a measure of cognitive effort was used to accurately distinguish alcohol-exposed subjects from controls and from subjects with ADHD with 77% and 73% classification accuracy, respectively (Dudley et al., 2012). While these findings are limited by the measures chosen for analysis, it is not surprising that clinically relevant deficits do not occur in all alcohol-exposed children. Any number of factors such as demographics, physiology, nutrition, or genetics, may result in a neuroprotective effect and warrant further investigation.

Measures of executive function were most effective in distinguishing AE subjects from controls. Because nearly all of the measures used in this phase of the CIFASD were from this domain, these results do not necessarily preclude the possibility that other cognitive domains might also be useful in classification. Future studies should include measures covering a broader array of neuropsychological domains. However, the fact that measures of executive function were effective in both of our studies suggests that this domain is especially affected in FASD. Further, these measures were also useful in distinguishing AE from ADHD, which has clear clinical significance.

Our study has many strengths, including the large heterogeneous sample from multiple sites, however, there are also limitations to our study. As mentioned, we focused mainly on measures of executive function, which, while critical for everyday function, are limited in

scope. Additional studies covering a broader array of neuropsychological domains and other types of data (e.g., including data on adaptive behavior, dysmorphology, or brain imaging) would enhance these results. Second, important differences resulted from our inclusion of the South African sample suggesting that variations on the profile may be more useful in accurately identifying alcohol-affected children at that site. Our groups were also not matched on demographic variables like race and ethnicity that were related to classification accuracy. However, the significant findings, in spite of such sample variability, make our results more powerful and generalizable. Further, the results of our follow up analyses including race, ethnicity, and age as covariates indicated that while important, these covariates did not change our ability to accurately classify AE subjects. An additional limitation is that we only included subjects without any missing neuropsychological data. However, our sample size is substantial even with this exclusionary criterion.

In summary, this study adds to the growing literature suggesting that the neuropsychological effects of AE are clinically meaningful and can be used to accurately distinguish alcohol-affected children from typically developing children. In addition, the results indicate that approximately 70% of children with heavy prenatal alcohol exposure are affected neurobehaviorally, even in the absence of FAS. The results also support previous studies showing differences between subjects with AE and those with ADHD. The ability to accurately distinguish these two groups has clear clinical significance; alcohol-affected children are highly likely to also have ADHD and thus may be clinically confused with non-exposed children with ADHD. The results of the current study indicate that while there are similarities, these two clinical conditions are not synonymous. Limited studies (Doig et al., 2008, Coe et al., 2001, Oesterheld et al., 1998, Frankel et al., 2006, O'Malley et al., 2000, Snyder et al., 1997, Collins et al., 2009) suggest differences in treatment effectiveness between FASD and ADHD, thus further indicating the need for accurate identification of alcohol-affected children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of neuropsychological variables included in analyses.

Observed Variable/Measure	Description	Functional Domain
Cambridge Neuropsychological Test Automated Battery (CANTAB)		
Delayed Matching to Sample Percent Correct - All Delays (z-score)	Percent correct matching of a novel pattern shown to one of four response options shown at a 4000ms or 1200ms delay	Short Term and Long Term Visual and Spatial Memory
Intra-Extra Dimensional Shift Stages Completed (z-score)	Number of rule change stages completed on a measure requiring adaptation to a series of changing conditions by recognizing variation of target stimuli	Executive Function, Cognitive Flexibility
Intra-Extra Dimensional Shift Total Errors (z-score)	Total number of errors made by failure to adjust to the novel conditions and properly attend to the correct features	Executive Function, Cognitive Flexibility
Simple Reaction Time Percent Correct Trials (raw score)	Raw score of reaction time, based on a correct button press to a stimulus	Attention, Reaction Time
Spatial Working Memory Total Errors (z-score)	Total number of errors (the return to a location where a stimuli was previously found)	Executive Function, Spatial Working Memory
Delis-Kaplan Executive Function System (D-KEFS)		
Color-Word Interference Inhibition/Switching (scaled score)	Time taken to complete switching between inhibitory responses and non- inhibited responses of color naming and word reading	Executive Function, Inhibitory Control, Cognitive Flexibility
Trail Making Test – Switching (scaled score)	Time taken to properly connect an alternating sequence of numbers and letters	Executive Function, Cognitive Flexibility
Twenty Questions Total Initial Abstraction (scaled score)	Measure of quality of the initial question asked, to reduce potential response options	Executive Function, Planning, Deduction
Tower Test Rule Violations per Item Ratio (scaled score)	Total number of rule violations produced per item ratio	Executive Function, Planning
Verbal Fluency Total Correct Letter (scaled score)	Total number of correct words produced over three different initial letter trials on the verbal fluency test	Executive Function, Fluency
Verbal Fluency Total Correct Switch (scaled score)	Total number of correct words produced during switching task(between fruit and furniture), regardless of switching accuracy, on the verbal fluency test	Executive Function, Cognitive Flexibility

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Table 2

Demographic data for subjects in the study groups used in the three analyses.[1]

	Exposed			Unexposed		
Variable	**AE (with FAS)**	**AE (without FAS)**	**AE (All)[2]**	**CON**	**ADHD**	**Group DIfferences**
N	79	117	209	185	74	
	M (SD)	**M (SD)**	**M (SD)**	**M (SD)**	**M (SD)**	
Age	12.37 (2.83)	12.71 (2.47)	12.55 (2.62)	12.28 (2.70)	11.37 (2.49)	AE vs. ADHD
IQ	69.15 (17.65)	78.09 (19.06)	74.52 (18.90)	99.12 (18.57)	95.19 (17.01)	AE/FAS & AE/Non-FAS vs. CON; AE vs. ADHD
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	
Sex (Female)	38 (48.1)	49 (41.9)	92 (44.0)	95 (51.4)	18 (24.3)	AE vs. ADHD
Handedness (Right)	69 (87.3)	103 (88.0)	185 (88.5)	175 (94.6)	67 (90.5)	
Site						
Atlanta	7	14	21	19	13	
Los Angeles	2	7	11	10	2	
Plains States	12	10	22	17	10	
New Mexico	2	4	12	18	10	
San Diego	11	37	53	60	39	
South Africa	45	45	90	61	0[3]	
Race (White)	22 (27.8)	37 (31.6)	143 (68.4)	100 (54.1)	56 (75.7)	AE/FAS & AE/Non-FAS vs. CON; AE vs. ADHD
Ethnicity (Hispanic)	1 (1.3)	10 (8.5)	16 (7.7)	26 (14.1)	18 (24.3)	AE/FAS vs. CON; AE vs. ADHD
Growth Deficiency[4,5]	55 (69.6)	52 (44.4)	107 (54.6)	30 (19.5)	7 (13.7)	AE/FAS & AE/Non-FAS vs. CON; AE vs. ADHD
Height ≤ 10%	45 (57.0)	45 (38.5)	90 (45.9)	20 (13.0)	5 (9.8)	
Weight ≤ 10%	48 (60.8)	45 (38.5)	93 (47.4)	19 (12.3)	5 (9.8)	
Microcephaly (OFC ≤ 10%)	66 (83.5)	45 (38.8)	111 (56.9)	19 (12.3)	4 (8.0)	AE/FAS & AE/Non-FAS vs. CON; AE vs. ADHD
Structural Abnormality[4,6]	79 (100)	29 (24.8)	108 (55.1)	16 (10.5)	8 (15.7)	AE/FAS & AE/Non-FAS vs. CON; AE vs. ADHD
PFL ≤ 10%	61 (77.2)	24 (20.7)	85 (43.6)	10 (6.5)	3 (6.0)	
Smooth	68 (86.1)	42 (35.9)	110 (56.1)	29 (19)	11 (21.6)	
Philtrum						
Thin Vermillion	71 (89.9)	33 (28.2)	104 (53.1)	26 (17)	9 (17.6)	
Border						
FAS Diagnosis	79 (100)	0 (0)	79 (40.3)	0 (0)	0 (0)	AE/FAS vs. CON

	Exposed			Unexposed		
Variable	**AE (with FAS)**	**AE (without FAS)**	**AE (All)[2]**	**CON**	**ADHD**	**Group DIfferences**
ADHD Diagnosis[3]	19 (57.6)	40 (62.5)	65 (60.2)	0 (0)	74 (100)	AE/FAS & AE/Non-FAS vs. CON; AE vs. ADHD

[1] Three sets of analyses were conducted. The first analysis included alcohol-exposed subjects (with FAS) and Control subjects. The second analysis included alcohol-exposed subjects (without FAS) and Control subjects. The third analysis included all alcohol-exposed subjects, and subjects with ADHD.

[2] The AE group includes 13 subjects without dysmorphology data that are not included in either the FAS or non-FAS groups.

[3] Children with ADHD were not recruited at the South African site.

[4] Dysmorphology examinations were conducted on 196 AE subjects, 154 CON subjects, and 51 ADHD subjects. Percentages are calculated using, as the denominator, the total available sample size.

[5] The presence of growth deficiency is defined as height or weight ≤ 10%.

[6] The presence of structural abnormality is defined as two or more of the following facial features: short palpebral fissure length, smooth philtrum, thin vermillion border.

Table 3

Descriptive Data for neuropsychological tests for subjects in the study groups used in the three analyses. Results of univariate analyses for these data can be found in the supplemental table.

	Exposed			Unexposed	
Observed Variable/Measure	**AE (with FAS)**	**AE (without FAS)**	**AE (All)**	**CON**	**ADHD**
	M (SD)	**M (SD)**	**M (SD)**	**M (SD)**	**M (SD)**
Cambridge Neuropsychological Test Automated Battery (CANTAB)					
Delayed Matching to Sample Percent Correct - All Delays (z-score)	0.01 (0.89)	0.03 (1.03)	−0.01 (1.00)	0.56 (0.87)	0.10 (0.93)
Intra-Extra Dimensional Shift Stages Completed (z-score)	0.01 (0.84)	0.11 (0.88)	0.05 (0.85)	0.32 (0.75)	0.20 (0.87)
Intra-Extra Dimensional Shift Total Errors (z-score)	−0.52 (0.97)	−0.07 (1.03)	−0.27 (1.03)	0.21 (1.04)	−0.09 (1.13)
Simple Reaction Time Percent Correct Trials (raw score)	97.99 (3.25)	97.68 (3.07)	97.52 (3.97)	98.69 (2.13)	96.19 (11.58)
Spatial Working Memory Total Errors (z-score)	−0.45 (0.79)	−0.20 (0.73)	−0.31 (0.77)	0.431 (0.79)	0.06 (0.76)
Delis-Kaplan Executive Function System (D-KEFS)					
Color-Word Interference Inhibition/Switching (scaled score)	6.33 (4.02)	7.40 (3.70)	6.97 (3.84)	10.47 (2.51)	9.50 (3.15)
Trail Making Test – Switching (scaled score)	4.80 (3.79)	5.55 (3.95)	5.29 (3.94)	9.10 (3.64)	7.77 (4.50)
Twenty Questions Total Initial Abstraction (scaled score)	6.47 (2.52)	7.10 (2.63)	6.86 (2.56)	9.64 (3.66)	9.57 (3.42)
Tower Test Rule Violations per Item Ratio (scaled score)	6.92 (3.26)	7.86 (2.84)	7.48 (3.05)	9.38 (2.13)	8.58 (2.76)
Verbal Fluency Total Correct Letter (scaled score)	6.01 (3.28)	7.52 (3.41)	7.05 (3.43)	10.17 (3.35)	10.22 (3.23)
Verbal Fluency Total Correct Switch (scaled score)	8.15 (3.51)	8.40 (2.97)	8.26 (3.25)	11.09 (3.01)	9.09 (2.83)

Table 4

Conditional response means and effect size differences between profiles based on the first analysis comparing alcohol-exposed (with FAS) subjects and controls.

Observed Variable/Measure	Profile 1	Profile 2	Cohen's *d*
CANTAB			
Delayed Matching to Sample Percent Correct - All Delays (z-score)	−0.23	0.81	1.35
Intra-Extra Dimensional Shift Stages Completed (z-score)	−0.10	0.44	0.71
Intra-Extra Dimensional Shift Total Errors (z-score)	−0.56	0.35	0.95
Simple Reaction Time Percent Correct Trials (raw score)	97.60	99.06	0.55
Spatial Working Memory Total Errors (z-score)	−0.51	0.62	1.65
D-KEFS			
Color-Word Interference Inhibition/Switching (scaled score)	6.88	10.79	1.22
Trail Making Test – Switching (scaled score)	3.93	10.38	2.38
Twenty Questions Total Initial Abstraction (scaled score)	6.05	10.44	1.57
Tower Test Rule Violations per Item Ratio (scaled score)	6.81	9.86	1.21
Verbal Fluency Total Correct Letter (scaled score)	6.38	10.61	1.32
Verbal Fluency Total Correct Switch (scaled score)	8.25	11.52	1.01

Table 5

Descriptive Data for neuropsychological tests by group for the second analysis comparing alcohol-exposed subjects (without FAS) and controls.

Observed Variable/Measure	Profile 1	Profile 2	Cohen's *d*
CANTAB			
Delayed Matching to Sample Percent Correct - All Delays (z-score)	−0.22	0.82	1.24
Intra-Extra Dimensional Shift Stages Completed (z-score)	−0.11	0.51	0.81
Intra-Extra Dimensional Shift Total Errors (z-score)	−0.42	0.52	1.01
Simple Reaction Time Percent Correct Trials (raw score)	97.39	99.03	0.64
Spatial Working Memory Total Errors (z-score)	−0.41	0.68	1.76
D-KEFS			
Color-Word Interference Inhibition/Switching (scaled score)	7.70	10.57	0.92
Trail Making Test – Switching (scaled score)	4.59	10.28	1.93
Twenty Questions Total Initial Abstraction (scaled score)	6.48	10.43	1.41
Tower Test Rule Violations per Item Ratio (scaled score)	7.48	9.86	1.02
Verbal Fluency Total Correct Letter (scaled score)	7.19	10.74	1.15
Verbal Fluency Total Correct Switch (scaled score)	8.74	11.23	0.79

Table 6

Conditional response means and effect size differences between profiles based on the third analysis comparing alcohol-exposed subjects (with and without FAS) and ADHD.

Observed Variable/Measure	Profile 1	Profile 2	Cohen's *d*
CANTAB			
Delayed Matching to Sample Percent Correct - All Delays (z-score)	−0.30	0.36	0.71
Intra-Extra Dimensional Shift Stages Completed (z-score)	−0.08	0.26	0.40
Intra-Extra Dimensional Shift Total Errors (z-score)	−0.55	0.12	0.67
Simple Reaction Time Percent Correct Trials (raw score)	96.86	97.51	0.09
Spatial Working Memory Total Errors (z-score)	−0.58	0.18	1.12
D-KEFS			
Color-Word Interference Inhibition/Switching (scaled score)	5.66	9.71	1.22
Trail Making Test – Switching (scaled score)	2.90	9.13	2.22
Twenty Questions Total Initial Abstraction (scaled score)	5.91	9.32	1.35
Tower Test Rule Violations per Item Ratio (scaled score)	6.45	9.16	1.01
Verbal Fluency Total Correct Letter (scaled score)	5.91	9.96	1.36
Verbal Fluency Total Correct Switch (scaled score)	7.78	9.51	0.55