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Neurodevelopmental Outcomes Associated with Prefrontal Cortical Deoxygenation in Children with Fetal Alcohol Spectrum Disorders

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ABSTRACT

Relationships between neurodevelopmental functioning and hemodynamic changes in the prefrontal cortex (PFC) were contrasted between children with prenatal alcohol exposure (PAE) and children who differed relative to their history of PAE and the presence of other neurodevelopmental impairment. For all groups, deoxygenated hemoglobin (HBR) levels in the medial PFC area were negatively related to externalizing problems and levels in the medial and right lateral PFC were positively related to errors on a cognitive inhibition task. Hemodynamic changes in the medial and right lateral PFC of children with PAE demonstrated stronger relationships to aspects of executive functioning relative to contrast groups.

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Introduction

Fetal Alcohol Spectrum Disorders (FASDs) (Riley, Infante, & Warren, 2011) is a term used to characterize a broad range of physical and neurodevelopmental sequalae associated with prenatal alcohol exposure (PAE). Since the original publication on Fetal Alcohol Syndrome (Jones & Smith, 1973), over 45 years have elapsed during which human and animal models have been used to identify the range of symptoms and explore the mechanisms by which PAE adversely impacts fetal development. Although many resources have been directed to preventing PAE, conservative estimates of the prevalence of FASDs have ranged from 1% to 5.0% (May et al., 2018) and difficulties with identifying these individuals persist (Chasnoff, Wells, & King, 2015).

Children with a history of PAE have an array of neurodevelopmental symptoms (Kable et al., 2016), including deficits in a cluster of EF skills known as executive functions (EF). Such skills have been found to differentiate children with PAE from both typically developing children and those with other clinical conditions (Mattson et al., 2013). These problems manifest in several ways in everyday functioning, including incorporating feedback to correct a response (Green et al., 2009), making errors on learning tasks (McGee, Schonfeld, Roebuck-Spencer, Riley, & Mattson, 2008), having difficulty making reversal shifts while learning (Coles et al., 1997; Green et al., 2009), impairments in verbal fluency (Vaurio, Riley, & Mattson, 2008), and inhibiting impulses (Kodituwakku et al., 2006). Behavioral and emotional control problems also are often reported by caregivers of children with FASD (Floyd, Weber, Denny, & O'Connor, 2009; Mattson & Riley, 2000).

Evidence suggests that the prefrontal cortex (PFC) (O'Hare et al., 2009) and the connectivity of the PFC to other brain regions (Wozniak et al., 2013) are adversely impacted by PAE and this may play a critical role in the expression of the commonly observed neurodevelopmental impairments.

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Further exploration of PFC activity that supports neurodevelopmental functioning in these children may aid in our ability to identify effective treatment strategies. However, imaging can be a problem for young children with FASD. Both heighten anxiety related to the scanner used to obtain the data and difficulties with the requirement to remain still during the assessment can affect results. Thus, traditional neuroimaging procedures, such as MRI, fMRI, and PET, can limit the age range of the children and the severity of the neurodevelopmental impairment that can be sampled. Other methods of visualizing hemodynamic changes in the brain may hold promise.

Functional near-infrared spectroscopy is an alternative to traditional neuroimaging methods that can be used to assess functional activity in the PFC (Ferrari & Quaresima, 2012). The fNIRS device used to obtain the estimates of the hemoglobin levels is placed directly onto the head, reducing movement-artifacts that often result in subject attrition, particularly among younger children (Soltanlou, Sitnikova, Nuerk, & Dresler, 2018), and allows the child to sit while performing a task. FNIRS takes advantage of the fact that infrared light, ranging from 650 to 1000 uv, is nearly transparent through human tissue but is differentially absorbed by oxygenated (HBO) and deoxygenated (HBR) hemoglobin (Ferrari & Quaresima, 2012). Using the modified Beer-Lambert Law (MBLL) (Kocsis, Herman, & Eke, 2006) estimates of relative changes in blood oxygenation in the PFC may be obtained by placing sensors on the scalp strategically located from the light emission. Validation studies comparing fNIRS and fMRI find good agreement between these methods (Amyot et al., 2012; Heinzel et al., 2013). Indices of brain functioning obtained from fNIRS have been found to differentiate clinical groups (Ishii-Takahashi et al., 2014; Kable & Coles, 2017; Wiley & Riccio, 2014), to be related to measures of behavioral functioning (Perlman, Luna, Hein, & Huppert, 2014), to be sensitive to the impact of pharmacological intervention (Monden et al., 2012), and has been recommended as a promising tool for improving our understanding of neuropsychiatric disorders (Ehlis, Schneider, Dresler, & Fallgatter, 2014).

In our previous work (Barrett, Kable, Madsen, Hsu, & Coles, 2019; Kable & Coles, 2017), we used fNIRS to assess hemodynamic changes in the PFC in children with a history of PAE (PAE group) and compared them to children without PAE who were either typically developing (Control group) or had clinically significant levels of developmental, learning, or behavioral problems (Clinical Contrast group). Using a task that assessed sustained attention and cognitive inhibitory control, PAE children were found to have reduced PFC HBO and increased HBR relative to both other groups in the inhibitory condition, suggesting reduced neural activity but increased oxygen consumption and poor replenishment (Barrett et al., 2019). In another task that elicited emotional arousal and the associated PFC inhibitory responses needed to modulate the arousal (Perlman et al., 2014), children with PAE had less activation during conditions with positive emotional arousal, as indicated by lower levels of HBO in the medial areas of the PFC and higher levels of HBR in all areas of the PFC relative to both other groups. Again, indicating a problem with oxygen replenishment during active neural engagement of the PFC (Kable & Coles, 2017).

In this current study, we have expanded the sample size from our earlier publications and extended the results to evaluate the relationships between the indices of PFC activity elicited under conditions of emotional arousal and the child's level of neurodevelopmental impairment to determine if these relationships were uniquely predictive of common neurodevelopmental deficits found in children with FASDs. We are particularly interested in the changes in HBR levels of the PFC during emotional arousal as these changes seemed to be pervasive across the PFC and may be indicative of disruption to angiogenesis that has been associated with PAE in animal models, including reduced vascular tissue and disrupted organization of cortical microvasculature (Jegou et al., 2012).

To achieve these goals, we could look at simple linear relationships with FASD children only but we are also interested in determining if levels of HBR during activation of the PFC could be used to differentiate children with FASDs from other groups of children and if these changes reflect a unique pattern of neural pathology that predicts prenatal alcohol-related impairment. To evaluate this, we will contrast the linear relationships between the HBR levels and neurodevelopmental outcomes

known to be impacted in children with FASD to relationships between these variables collected in both typically developing children and those with other neurodevelopmental disabilities who might present for clinical care. The lack of effective biomarkers has resulted in many children with FASD not being appropriately identified (May et al., 2018) or being misclassified (Chasnoff et al., 2015) and is of concern given that there is evidence of differential treatment responsiveness (Kable et al., 2016).

Based on our previous findings, relationships between hemodynamic changes of HBR levels and neurodevelopmental outcomes in the PFC of children with FASD were hypothesized to differ from those of children who did not have a PAE history and were either typically developing or had other neurodevelopmental disabilities of unknown origin. In particular, higher levels of HBR while performing tasks that elicit PFC activation in children with FASD were anticipated to be more strongly related to their level of neurodevelopmental impairment than the contrast groups, reflecting an underlying disruption to oxygenation.

Materials and methods

Participants

Eighty children between the ages of 5 and 18 years from the Atlanta metropolitan area were enrolled into the study. The children were recruited from a pool of children who were seen as part of a multisite collaborative project that identified neurodevelopmental characteristics that were distinctive of children with FASD as compared to other children. A consent procedure approved by the Human Subjects Committee of the Emory University School of Medicine was conducted, including a separate consenting procedure for the fNIRS assessment. Participants were reimbursed for their time. Exclusionary criteria included being non-fluent in English, having a history of significant head injury or loss of consciousness (> than 30 min), a history of adoption outside of the United States after age 5 or 2 years before the assessment, evidence of other known causes of mental deficiency, or having a psychiatric or physical disability that interfered with the study's assessments. Recruitment and procedures were in accordance with the Declaration of Helsinki guidelines.

Criteria for the prenatal alcohol-exposed (*PAE*) group ($n = 33$) was having a history of heavy PAE (>4 drinks/occasion or >13 drinks/week during pregnancy) or when such exposure was suspected in a child with a clinical FASD diagnosis using the Emory diagnostic classification (Coles et al., 2016). Criteria for the comparison sample of non-alcohol-affected children, or *Control Group (CON, $n = 25$)*, included having a reliable history of minimal (<1 drink/week, never >2 drinks/occasion) or no alcohol exposure in pregnancy and no clinically significant emotional or behavioral parental concerns about the child at the time of enrollment. Finally, an additional comparison sample of children was recruited who met the same requirement of no PAE as did the Control Group but who had identified developmental, learning or emotional/behavioral problems, the *Clinical Contrast Group* (CC) ($n = 22$). Clinically significant levels of concern regarding behavioral and emotional functioning were defined as seeking assistance from a primary doctor or mental health professional regarding a behavioral problem or having a specific neurodevelopmental or mental health diagnosis or concern based on parent report at the time of enrollment.

Participants were recruited from multiple sources, including a multidisciplinary team clinic established to evaluate children with a history of alcohol and drug exposure, siblings of those seen in this clinic, a waiting room of a child psychiatry clinic, and community education and health programs. A Health Insurance Portability and Accountability Act (HIPAA) partial waiver was used to recruit participants from the multidisciplinary clinic. To make a diagnosis on the fetal alcohol spectrum, the clinic conducts neurodevelopmental testing and a physical examination using a standard pediatric dysmorphia checklist (Fernhoff, Smith, & Falek, 1980) that weights symptoms based on their saliency for the diagnosis (e.g., hypoplastic philtrum is a "3"). Additional details regarding the diagnostic procedures of the clinic are published elsewhere (Coles et al., 2016). PAE histories were obtained through retrospective maternal report or social service, legal, or medical

records. In cases where this information was not available but prenatal alcohol exposure was suspected and the participant met criteria for FAS symptoms in three domains (dysmorphia, growth delays, and neurodevelopmental impairment), subjects were included in the PAE group.

The PAE group consisted of 16 (48.5%) with a fetal alcohol spectrum disorder diagnosis and 17 (51.5%) recruited from the community and identified as having heavy PAE. Parental report among this group of children indicated that 24 children had behavioral problems and 13 had a significant learning or developmental problem. Among the Controls, none of the children assigned to the group was identified by their parents as having significant learning or developmental problems but four were identified as having behavioral problems. Two parents indicated concerns with their child's hyperactivity, one expressed concern regarding their child's acting out, and one expressed concern about their child crying too frequently but none had sought out professional consultation. Among the Clinical Contrast group, 18 were identified by their parents as having a significant behavioral problem and 5 were identified as having a significant learning or developmental problem. Portions of the Diagnostic Interview Schedule for Children, IV (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) were used to further characterize the sample but not for the purposes of group assignment. The results are in Table 1. Both the PAE and Clinical Contrast groups had significantly more endorsements of a psychiatric disorder than did those in the Control group.

Behavioral problems

To assess the child's behavioral functioning, parents completed the Child Behavior Checklist (CBCL) (Achenbach, 2009), which is a well-established measure of child emotional and behavioral functioning that has been repeatedly found to be sensitive to behavioral dysfunction found in children with FASDs (Tsang, Lucas, Carmichael Olson, Pinto, & Elliott, 2016). The questionnaire consists of multiple problem behaviors that are rated as "not true," "sometimes true," or "very true." Items are clustered into subscales, which are then aggregated into three summary scores, a Total Problems scores as well as summary scores for Internalizing and Externalizing Problem Behaviors. Scores are reported in terms of T-score relative to a reference sample with a mean of 50 and standard deviation of 10 points with higher scores reflecting more behavioral disturbance. Only the Externalizing and Internalizing Problem Behaviors summary scores from the CBCL were used for linear relationship analysis as the Total Problem Behaviors score represents a summary of problem behaviors from both domains.

Child executive functioning

The child's executive functioning skills were assessed using portions of the NEPSY-2 (Korkman, Kirk, & Kemp, 2008). The test is a well-established standardized measure of EF that can be administered to children whose ages span from the preschool period to late adolescences. Specific subtests sampled were the Inhibition, Speeded Naming, and Word Generation tasks. Each of the tasks assesses some component of EF and performance on each of the tasks are scored relative to nationally standardized normative samples. Performance is reported in terms of scaled scores with means of 10 and standard deviation of 3 and are constructed so that higher scores reflect more optimal performance. Within each task, there are subscales for only older children but only scores from the subscales that were administered to the entire sample were used for this analysis. The Inhibition task assesses the participant's ability to inhibit an overlearned or habitual behavior and assesses cognitive inhibitory control. The Inhibition task is composed of three different components assessed across two different stimulus sets. The condition where the participant was asked to name the opposite condition of the stimulus presented, the Inhibition portion, and the standard score for errors were used for analysis. Children with FASD have historically been found to struggle with tasks that require cognitive inhibition (Connor, Sampson, Bookstein, Barr, & Streissguth, 2000; Ware et al., 2012) and deficits in this area have been linked to alterations in brain structure (Migliorini

Table 1. Sample characteristics by group status.

Measure	Controls n = 25	Prenatal Alcohol-Exposed n = 32	Clinical Contrast n = 20	Statistic and p-Value
Child's Age [M (SD)]	8.80 (3.4)	9.97 (2.9)	9.90 (3.2)	
Child's Gender (% male)	52%	42.4%	52.4%	
Race (% African American or Mixed Race/African American)	92.0%	84.8%	95.2%	
Ethnicity (% Non-Hispanic)	100%	84.8%	90.5%	
Parental Behavioral Concern (% yes)	16.0%	72.7%	85.7%	χ (2) = 27.703, $p < .0001$
Met DISC[a] Criteria for ADHD[b]	12.0%	54.5%	33.3%	χ (2) = 11.308, $p < .004$
Met DISC[a] Criteria for ODD[c]	4.0%	39.4%	38.1%	χ (2) = 10.363, $p < .006$
Met DISC[a] Criteria for CD[d]	0%	3.0%	0%	
Met DISC[a] Criteria for MD[e]	0%	3.0%	14.3%	
Met DISC[a] Criteria for GA[f]	0%	6.1%	4.8%	
Developmental or Learning Problem (% yes)	0%	39.4%	23.8%	χ (2) = 12.564, $p < .002$
Child Protective Service Involvement (% yes)	16.0%	30.3%	14.3%	
Placement				
Biological Parent (% yes)	88%	48.5%	85.7%	
Kinship Care (% yes)	8%	24.2%	9.5%	
Legal Guardian/Adoptive Parent (% yes)	4%	27.3%	4.8%	χ (4) = 14.353, $p < .006$
Mean Head Circumference[g]	54.2 (3.0)	52.1 (2.1)	53.1 (2.5)	(F (2, 66) = 4.16, $p < .020$)
Mean Head Circumference Percentile[g]	72.0 (31.9)	38.1 (32.7)	51.2 (34.7)	(F (2, 66) = 6.42, $p< .003$)
Mean Weight Percentile[g]	68.7 (28.2)	54.8 (28.2)	58.1 (28.6)	
Mean Height Percentile[g]	60.7 (30.8)	40.5 (30.6)	44.6 (30.0)	
DAS GCA[h] [M (SD)]	92.48 (10.2)	85.24 (12.3)	80.57 (12.0)	(F (2, 76) = 6.24, $p < .003$)

[a]Diagnostic Interview Schedule for Children (DISC (Shaffer et al., 2000)); [b]Met criteria for an Attention-Deficit Hyperactivity Disorder; [c]Met criteria for an Oppositional-Defiant Disorder on the DISC; [d]Met criteria for a Conduct Disorder on the DISC; [e]Met criteria for a Major Depression/Dysthiamia Disorder on the DISC; [f]Met criteria for a Generalized Anxiety Disorder on the DISC; [g]Data only available on a subset who returned for the physical dysmorphia examination (n = 69); [h]DAS GCA refers to the Differential Ability Scale's General Conceptual Ability (Elliot, 2007) score, which is measure of overall intelligence with a Mean of 100 and standard deviation of 15.

et al., 2015). The Speeded Naming subtest requires the participant to name common stimuli (colors, shapes, letters, and numbers) and their characteristics (i.e. big red circle) as rapidly as possible, which is recognized as a measure of rapid semantic processing. These tasks has been found to differentiate neuropsychological impairments found in children with FASDs (Rasmussen et al., 2013). The combined scores that integrate both successful performance and speed were selected as outcomes from these two subtests. Finally, the Word Generation task requires the participant to generate rapidly words from given criteria to assess verbal productivity. FASD children have been found to perform poorly on similar tasks (Vaurio et al., 2008) and deficits in this area have been predictive of functional communication impairments in children with FASDs (Doyle et al., 2018).

FNIRS procedures

Hemodynamic changes in brain functioning were measured using Biopac Model # FNIRS 100B, which is a neuroimaging device placed on the forehead of the participant that was developed by *FNIR Devices*. The system consisted of a pad containing 4 light-emitting diodes (LEDs) and 10 sensors that cover the forehead of the participant, a control box for data acquisition, a power supply, and a laptop for the data encoding and analysis. Near-infrared light absorption data were collected using Cognitive Optical Brain Imaging (COBI) Studio (Ayaz et al., 2011) during computer game play. The pad contained a reusable, flexible circuit board that contained the

LEDs, sensors, and a cushioning material that attached the sensor to the participant. The center of the pad was placed at the participant's nasion point and secured to the head using Velcro wraps. Source-detector separation was 2.5 cm (Ayaz et al., 2011). LED lights were presented with a time sequence of 50 msec at wavelengths of 730 nm and 850 nm to estimate simultaneously HBO and HBR levels. Data were collected across 16 optodes across the forehead and a 10-second baseline was collected at the start of the experiment that was used as a referent for estimating changes in PFC functioning during task performance. As a result, values of HBO and HBR may be either positive or negative.

FNIRS signals were processed, analyzed, and visualized using FNIRSoft Professional Edition from Drexel University (Ayaz, Izzetoglu, Shewokis, & Onaral, 2010). MBLL was used to estimate the concentration of the HBO and HBR from the light intensity. Preprocessing of the data was done to remove data artifacts. First, a finite impulse response linear low pass filter was applied with an order of 20 and a cutoff frequency of 0.1 Hz to isolate the near-infrared signals from other background physiological signals (i.e. heart rate and respiration) and then a median filter was used. The median filter used a window size of 25 and applied discrete window-based median filter to each optode coupled with an optional finite impulse response filter. An algorithm, the Sliding-window Motion Artifact Rejection (SMAR) (Ayaz et al., 2010, 2011), was then applied to remove motion artifacts in the signal with a window size of 10. Estimates of HBO and HBR were then computed from the cleaned data using MBLL and a detrending procedure was used to eliminate time sampling measurement errors. This procedure applies a first-order linear detrending to each optode to eliminate the slope of the overall vector time-series.

For purposes of this study, only HBR levels will be used as this measure was most sensitive to the effects of PAE in our previous research (Barrett et al., 2019; Kable & Coles, 2017) and may reflect underlying disruption of vascular development identified in an animal model of PAE (Jegou et al., 2012). HBR levels reflect the amount of hemoglobin that has relinquished its oxygen. Higher levels of HBR may reflect less neural activation as long as the HBO levels are the same or are reduced but may also reflect changes in the total blood volume content or ratio of HBO to HBR (Villringer, 1997). During increased neural activation, HBR levels are anticipated to generally decrease as increased levels of HBO are brought in to meet the needs of the active neural tissue. Increased levels of HBR during neural activation, as indicated by increased levels of HBO, reflect a potential buildup of HBR, which may limit the oxygen supply needed for subsequent neural activation.

FNIRS task

Prefrontal cortical brain activation was assessed while completing a computer task, the *Frustration Emotion Task for Children (FETCH)* (Perlman et al., 2014), which involves the child competing to retrieve a bone before the computerized dog retrieves the bone. The game alternates blocks where the child can either be successful or not. Blocks 1, 3, and 5 are referred to as Win blocks where the child can make a response before the dog on five of the six trials. Blocks 2, 4, and 6 are referred to as Loss blocks where the child is unable to make a response before the dog on five of six trials. Each of these blocks last 10,000 ms and has a delay and rest phase combined interval of 6,000 ms. Additional details regarding the task are available (Kable & Coles, 2017). HBO and HBR data for each block were aggregated across each of the conditions (Win or Loss) and exported for data analysis. Data were further aggregated across optodes with eight optodes in the center formulating one index (Medial) and the four optodes combined on left and right sides to assess lateral PFC activity (Right Lateral and Left Lateral). Finally, indices of PFC activity (HBO and HBR) were aggregated across the 120 time samples collected for the Win and Loss conditions to formulate on overall mean for each respective condition for the three areas.

Analytic plan

Statistical analysis was carried out using SPSS 24.0. Group differences in characteristics of the individuals and the families in which they reside were examined using descriptive statistics and frequency distributions. The Potthoff regression procedure (Potthoff, 1978), which allows for simultaneous and separate tests of regression intercepts and slopes across groups, was performed. The Potthoff regression procedure is recognized as an efficient and parsimonious regression procedure that allows for both simultaneous and separate tests of regression slopes and intercepts across groups (Watkins & Hetrick, 1999) within one analysis as opposed to running multiple comparisons of slopes derived from estimating each group independently. The procedure is conducted by creating dummy code variables for each of the groups and computing interaction terms for each group's dummy code variable and the HBR level. The first step in the model evaluated in the procedure is the linear relationship between HBR levels and the neurodevelopmental outcome variable. The second step in the model, detailed below, contrasts the beta weights of the Control group relative to the PAE and Clinical Contrast groups and their interaction with HBR levels after removing variance accounted for in the neurodevelopmental outcome by the grouping variables alone. Interaction terms (HBR by PAE and HBR by Clinical Contrast group) are entered simultaneously in the model. An additional contrast then evaluated the PAE and the Clinical Contrast groups from each other. The beta weights (β_x) for the interactions reflect the slopes found in the linear relationship between variables.

$$\text{Neurodevelopmental Outcome} = \beta_0 + \beta_1(\text{PAE STATUS}) + \beta_2(\text{Clinical Contrast STATUS}) + \beta_3(\text{HBR level} * (\text{PAE STATUS})) + \beta_4 \text{Group}(\text{HBR level} * (\text{Clinicial Contrast STATUS}))$$

Within each PFC region (lateral left, medial, and lateral right), we evaluated 12 models consisting of HBR levels obtained from two conditions (Win or Loss) and predicting to six neurodevelopmental outcomes. Comparisons between groups were *a priori* contrasts within the model. We hypothesized that HBR levels will predict neurodevelopmental impairment and that this relationship in the PAE group would be characterized by higher HBR levels having stronger relationships with neurodevelopmental impairment as compared to both other groups of children. Simple Pearson correlations are also provided for the linear relationships. Each of the indices (r and β_x) reflect different aspects of the linear relationship with Pearson correlations reflecting the dispersion of the data relative to the regression line and the beta weights from the Potthoff regression procedure reflecting the slope of the regression line. Selected figures are presented to illustrate variations in these relationships.

Results

Group characteristics

One participant's PFC data from the FETCH task could not be used as result of computer malfunction and two participant's caregivers did not complete the CBCL. Table 1 contains further details regarding the sample characteristics. Children's current placement or caregiver varied as a function of group status (χ (4) = 14.353, $p < .006$) but they did not differ on other demographic characteristics or involvement with child protective services. Among children in the Control group, 88.0% were living with a biological parent while only 48.5% of the children with PAE were with a biological parent. The other children in this group were living with a relative (24.2%) or a legal guardian/adoptive parent (27.3%). For the Clinical Contrast group, 85.7% of the children were with a biological parent, 9.5% were with a relative, and 4.8% were living with a legal guardian/adoptive parent. Global cognitive ability as assessed by the Differential Ability Scales, 2nd edition (Elliot, 2007) also differed by group status (F (2, 76) = 6.24, $p < .003$) with the Control group (M = 92.48 (SD = 10.2)) performing significantly higher than those in the Clinical Contrast group (M = 80.57 (SD = 12.0)) and the PAE group (M = 88.24 (SD = 12.3)), which did not differ from each other.

A subset (n = 69) of the participants had physical growth measurements collected as part of the larger multi-site project and the mean values are also in Table 1. The participants did not differ in their body weight or length but did have differences in the head circumference with those in the PAE and the Clinical Contrast group having smaller head sizes than did the Control children on both the mean percentile (F (2, 66) = 6.42, p < .003) and the absolute values of the head size (F (2, 66) = 4.16, p < .020). A preliminary examination was done relating the head circumference values and percentiles to the HBR levels obtained from each of the three aggregated areas of the PFC but the relationships were not significant so no further adjustments were made in the analysis for the differences in head size.

Group differences in neurobehavioral characteristics

Means and standard deviations of the neurobehavioral outcomes for each of the groups are displayed in Table 2. On the CBCL, a significant group effect was found on the Externalizing Problem Behavior (F (2, 74) = 23.845, p < .000, CON < CC, PAE) but not on the Internalizing Problem Behavior (F (2, 74) = 2.504, p < .089). The PAE and the Clinical Contrast group received higher scores relative to those in the Control group but did not differ from each other. Relative to child EF skills, group difference was found on the standard scores for Total Errors on the Inhibition task (F (2, 63) = 5.982, p < .004) with those in the PAE group performing lower than did those in the other two groups. Group differences were also found on the Speeded Naming Combined score (F (2, 76) = 3.148, p < .049) with those in the Clinical Contrast group performing more poorly than did Control group.

Group differences in the slope of the relationship between indices of neural activation and neurodevelopmental dysfunction

Table 3 contains the beta weights, their standard errors, and the simple Pearson correlations for the significant models and their associated effects. Group by HBR changes in the Lateral Left PFC were not significant for any of the models and there were no significant models for predicting Internalizing Problem Behaviors, Speeded Naming, or the Inhibition Total Score for any brain area. Significant relationships for HBR levels predicting Externalizing Problem Behaviors, Inhibition Errors, and Word Generation scores were found. The results that were uniform across groups, indicating common underlying relationships, are reported first followed by group differences in the slopes of the relationships.

Uniform relationships between HBR levels and neurodevelopmental outcomes

Levels of HBR in the PFC demonstrated significant linear relationships between neurodevelopmental outcomes that were uniform across groups. Externalizing scores on the CBCL were negatively related to Medial HBR levels in both the Win (r = −.273, p < .016) and Loss (r = −.249, p < .029, see Figure 1 for illustration) conditions with no significant differences in slope between the groups, suggesting a common underlying pathology linking the dispersion within the linear relationships. In addition,

Table 2. Neurobehavioral outcomes as a function of group status.

	Controls (CON), n = 25	Prenatal Alcohol-Exposed (PAE), n = 32	Clinical Contrast (CC), n = 20	Group Comparisons
Child Behavior Checklist Summary Scores				
Internalizing	52.0 (9.1)	57.9 (9.9)	55.3 (10.6)	
Externalizing	45.7 (9.0)	61.1 (8.1)	59.5 (9.6)	Con < CC, PAE
NEPSY-2 Executive Functioning Scores				
Inhibition Combined	7.5 (3.3)	5.5 (3.4)	7.0 (3.2)	
Inhibition Total Errors	6.8 (3.7)	3.7 (3.2)	6.7 (4.2)	PAE < CC, CON
Speeded Naming Combined	9.0 (2.7)	7.7 (2.2)	7.1 (2.9)	CC < CON
Word Generation Semantic	9.8 (3.4)	8.9 (4.1)	8.4 (3.5)	

Table 3. Slope, Standard Mean Error of the Slope, and Pearson Correlations of the significant relationships between changes in deoxygenated hemoglobin in the prefrontal cortex and neurodevelopmental outcomes.

			Controls, (CON) *n*= 25	Prenatal Alcohol-Exposed (PAE) *n*= 32	Clinical Contrast (CC) *n*= 20		
PFC	Neurobehavior	Condition	Slope (Error)	Slope (Error)	Slope (Error)	Direction of Effects	Simple Pearson's
Right	Externalizing	Loss	−4.79 (2.0)	3.81 (2.4)	6.95 (2.5)	CC > CON	$r^{CON} = -.473$, $r^{CC} = .294$
	Inhibition Errors	Loss	1.18 (.75)	−0.82 (.92)	−0.11 (.94)	No Group Effects	$r^{ALL*} = .329$
	Word Generation	Win	0.36 (1.1)	−2.60 (1.2)	−0.04 (1.3)	PAE < CON, CC	$r^{PAE} = -.511$, $r^{CON} = .070$, $r^{CC} = .092$
Medial	Externalizing	Win	−4.27 (2.0)	2.83 (2.8)	−0.51 (2.9)	No Group Effects	$r^{ALL*} = -.273$
	Externalizing	Loss	−4.45 (1.7)	2.93 (2.4)	3.55 (2.1)	No Group Effects	$r^{ALL*} = -.249$
	Inhibition Errors	Loss	1.06 (.67)	−0.98 (.94)	−0.66 (.82)	No Group Effects	$r^{ALL*} = .279$
	Word Generation	Win	0.16 (.89)	−2.43 (1.2)	−0.38 (1.3)	PAE < CON	$r^{PAE} = -.437$ $r^{CON} = .038$ $r^{CC} = -.057$

*ALL refers to the correlation when all groups are aggregated and is reported when linear relationships exist but no group interactions were found between HBR levels and neurodevelopmental outcomes in the slope.

accuracy (or reduced errors) in performance on the Inhibition task were positively related to HBR levels obtained during the loss condition in both the Medial (r = .279, $p < .024$) and Right Lateral PFC (r = .329, $p < .007$) with no significant differences in the slopes of the groups.

Group differences in relationships between HBR levels and neurodevelopmental outcomes

A significant effect was obtained for an HBR level by group interaction (F (2, 73) = 3.998, $p < .023$) in the Win condition using HBR levels of the Right Lateral PFC for predicting Word Generation performance. The PAE group demonstrated significantly more negative slope relative to both other groups (CON: $t = -2.096$, $p < .04$; CC: $t = -2.540$, $p < .013$; see Figure 2 for illustration), suggesting that higher levels of HBR in the Right Lateral PFC were associated with a stronger decline in verbal fluency performance than was found in both other groups of children. A similar pattern was found in the Medial PFC and Word Generation Semantic score relationships but the interaction effect was only a trend (Interaction effect: F (2, 73) = 2.407, $p < .097$, Planned Contrast of PAE vs. CON: $t = 2.015$, $p < .048$). In the Loss condition, a significant group by HBR level interaction was found between the Right Lateral PFC and the Externalizing Problem Behaviors (F (2, 72) = 4.072, $p < .021$), which was characterized by the Clinical Contrast group having a more positive slope relative to the Control children ($t = 2.835$, $p < .006$) but neither group differing from the PAE group.

Discussion

The role that the PFC plays in mediating child neurodevelopmental functioning was explored using three different groups of children who differed relative to their history of PAE and the presence of neurodevelopmental impairment. The groups allowed for comparisons of the impact of PAE relative to typically developing children with no PAE and to those with a history of clinically significant problems who did not have PAE. The neurodevelopmental functioning of the children varied accordingly with the characteristics for which they were recruited but there was considerable overlap in the characteristics of children with a history of PAE and those with other clinical problems. Despite the overt behavioral overlap, the results of this study suggested that children with a history of PAE had unique characteristics in the relationships between the indices of PFC functioning and

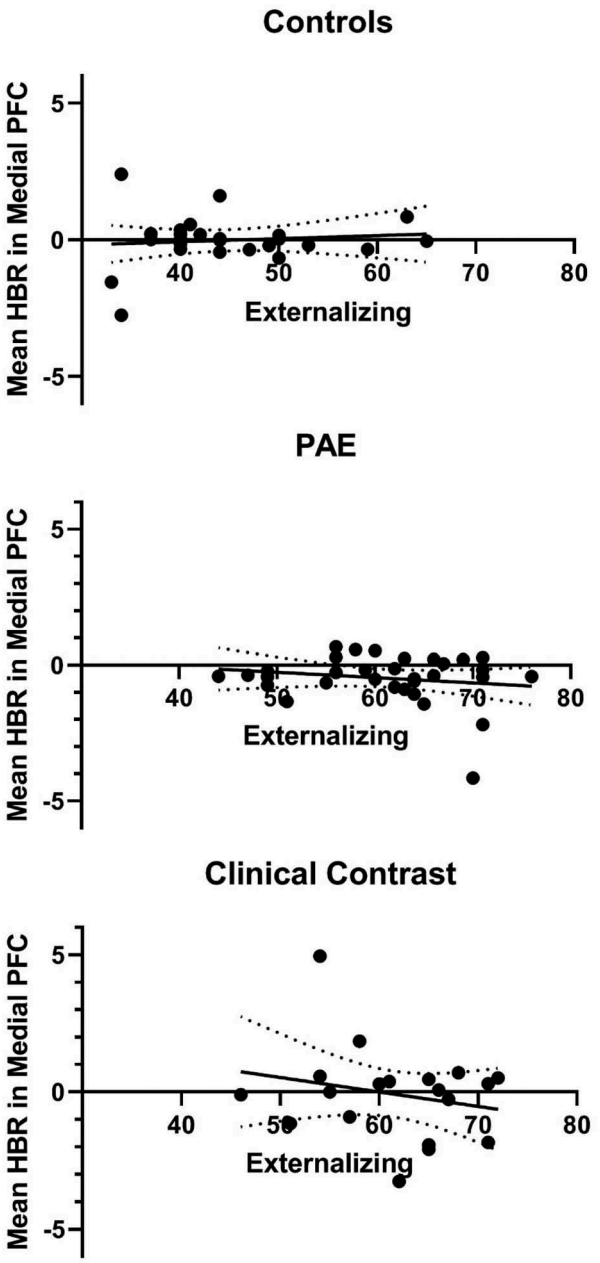

Figure 1. The plots of individual subject data and predicted lines of the relationship between mean HBR in the Medial PFC in the Loss condition relative to Child Behavior Checklist Externalizing t-scores by group status are represented. There were no group differences in the slopes of the linear relationship (r = −.249) between mean HBR in the Medial PFC and externalizing problem behavior scores [Control (slope = −4.45 (1.7)); PAE (slope = 2.93 (2.4); Clinical Contrast (slope = 3.55 (2.1))].

neurodevelopmental problems that may be useful in differentiating them from typically developing children and from those who have neurodevelopmental problems not associated with PAE.

Contrary to our hypothesis, uniformity across the three groups characterized the linear relationships between HBR changes in the Medial PFC and indices of externalizing problem behaviors and response accuracy on a cognitive inhibition task. For all participant groups, increased levels of HBR

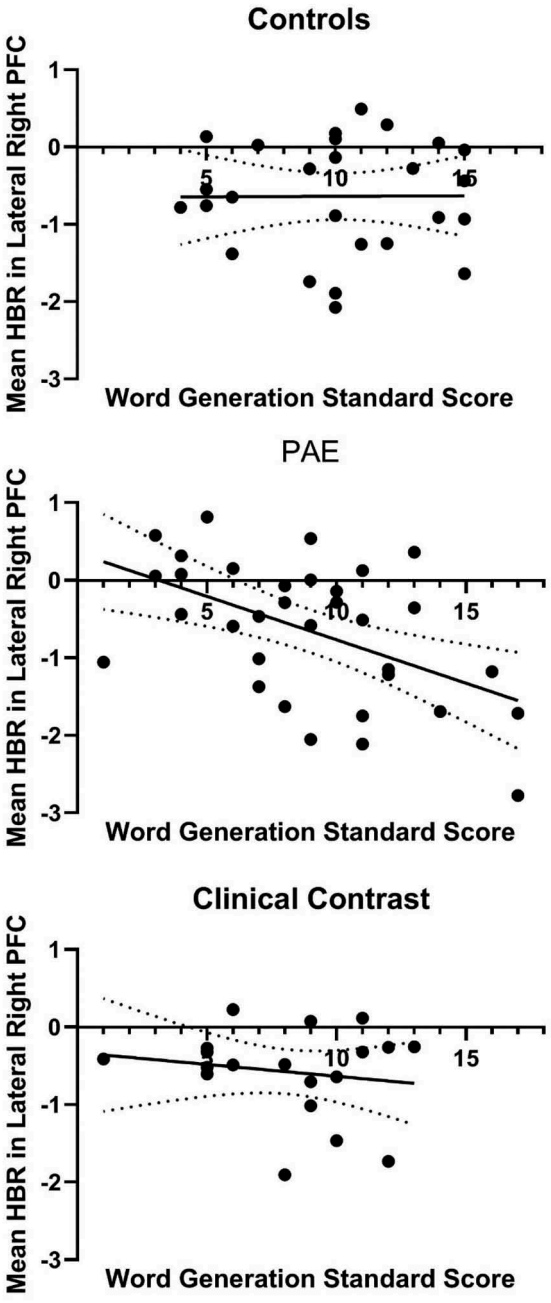

Figure 2. The plots of individual subject data and predicted lines of the relationship between mean HBR in the right PFC in the Win condition relative to Word Generation scores by group status are represented. The slope of the children with a history of PAE (slope = −2.60 (1.2) was significantly more negative than were the slopes for the other two groups of children [Controls (slope = 0.36 (1.1)) and Clinical Contrast (slope = 0.04 (1.3))].

during both arousal conditions were associated with lower externalizing problem behaviors and higher scores on a cognitive inhibition task but only for levels of HBR during the loss condition. HBR values in the Right Lateral PFC were also predictive of accuracy on the cognitive inhibition

task. Although HBR levels in the Medial PFC, an area known to be linked to reward processing (May et al., 2004) and self-monitoring (Davidson, Fox, & Kalin, 2007), may be linked to externalizing behaviors and cognitive inhibition deficits, these relationships do not appear to be unique characteristics to prenatal alcohol teratogenesis and may not serve as a useful biomarker for identifying individuals impacted by PAE.

In contrast, individuals in the PAE group demonstrated unique relationships between hemodynamic changes in the PFC during positive arousal and word fluency that was consistent with our hypothesis. Higher levels of HBR in the Right PFC were associated with poorer performance on a task of rapid word retrieval for the PAE group but this relationship was non-existent for the other two groups, suggesting that the buildup of HBR during positive arousal may be the most distinguishing characteristic of the PAE group. A trend was also found for a similar relationship for HBR levels in the Medial PFC but only the Control group differed from the PAE group. This pattern of relationship was not consistent across all areas of executive functioning skills but it is unclear whether this is the result of specificity in the word retrieval response or a limited power to detect smaller effects as a result of the sample size. Alternatively, the observed effect may be a false positive but this seems unlikely given that the relationship was comparable in two brain regions. Replications with larger sample sizes may be needed to clarify this.

In our previous work (Kable & Coles, 2017), HBR levels in the Win condition generated the strongest group differences for the PAE group relative to the other two groups of children so it is not surprising that in this larger sample these responses have stronger relationships with an EF outcome commonly found to be impaired in individuals with PAE (Rasmussen, 2005; Vaurio et al., 2008). Disruption of oxygen diffusion to the Right PFC during positive arousal may be an important marker for prenatal alcohol-related neurodevelopmental impairment as this group found that improved EF skills were associated with less buildup of HBR. This is a marked difference to those who have neurodevelopmental impairments not caused by PAE, the Clinical Contrast group, who demonstrated a pattern of Right Lateral PFC involvement in negative arousal relative to Controls that was predictive of their levels of emotional and behavioral disturbance. The Right Lateral PFC is an area of the brain linked to emotional and behavioral inhibition or suppression (Li, Grabell, Wakschlag, Huppert, & Perlman, 2017) and to the regulation of rule-breaking behavior (Possin et al., 2009).

Although the results of this study provide information regarding the linear relationships between hemodynamic changes in areas of the PFC and behavioral outcomes, these relationships do not necessarily imply causation. Other variables may play a role in influencing or even creating the observed relationships. Instead, it implies that changes in HBR levels while dealing with emotional arousal in children with FASD are a marker for underlying brain pathology that is predictive of their deficits in word fluency.

Although intellectual ability is often a confounding variable that differentiates children with FASD from other contrast groups, it is unlikely that this variable is contributing to the obtained group differences as on average, the Clinical Contrast group in this study also had mild cognitive impairment (> 1 SD from normative means). Other factors associated with the group differences in placement history cannot be ruled out as important mediators of the obtained relationships. This study, for the most part, utilized a clinical sample of children recruited because of their neurodevelopmental problems and replicating the relationships between behavioral and PFC functioning in a prospective sample of alcohol-exposed individuals would help in clarifying if PAE was mediating the differences in the relationships. As many trends were found that were not interpreted in this study, future studies may also need to expand the number of participants to increase the statistical power with which these relationships are evaluated as only moderate to large effects were able to be identified with the sample size and number of groups compared in the analysis.

Potential differences in the caregiver who rated the child's behavior are unlikely to have contributed to group differences in this study. Although there was a significant difference in the child's placement with 88% of Controls and 85.7% of the Clinical Contrast as compared to only 48.5% of those in the PAE group living with a biological parent, there were no group differences in behavioral

problem ratings on the CBCL between those seen in the PAE and Clinical Contrast group and both clinical groups differed from the controls as would be expected. There were also no PAE differences in relationships between the hemodynamic changes in the prefrontal cortex and behavioral functioning. Instead, the PAE group was differentiated from both other groups relative to their performance on standardized neurocognitive testing and in the relationships between their performances and the changes in the HBR levels in the Right Lateral PFC.

Variations in cortical depth and anatomical differences may play a role in producing the alterations in the estimates of the hemodynamic changes associated with brain functioning (Whiteman, Santosa, Chen, Perlman, & Huppert, 2018). Children with FASDs often have a reduced head circumference, which has been found to be correlated to the depth of the cortex (Whiteman et al., 2018), but head size was not found to be related to the aggregate measures of PFC functioning used in this study. Aggregation of the data across optodes may have minimized the impact of head circumference size as has been reported in other studies (Haeussinger et al., 2011; Whiteman et al., 2018). The infrared light used in fNIRS is only capable of being absorbed and appropriately reflecting back within a limited range into the cortex and therefore can only provide estimates of changes in blood oxygenation observed at the cortical surface level (Vanderwert & Nelson, 2014). Subcortical regions involved in inhibitory control, problem-solving, reward processing, and emotional regulation are not able to be sampled using this methodology. As the neurodevelopmental outcomes assessed are a diverse array of behaviors that are influenced by complex neural circuitry that supports the behavior and cannot be adequately sampled using this fNIRS methodology, complementary work with other neuroimaging methodologies will be needed to provide a detailed understanding of the brain–behavior relationships that are disrupted by PAE.

The neurodevelopmental functioning, specifically scores on measures of parent-rated problem behaviors on the Child Behavior Checklist (Achenbach, 2009) and child performance on EF tasks from the NEPSY-2 (Korkman et al., 2008), were related to the indices of hemodynamic change obtained from fNIRS. Although there were some consistent relationships across all groups, the groups differed in some of these relationships. Specifically, changes in Right Lateral PFC HBR levels in the Win condition differentiated the PAE group from both groups without PAE who either had or did not have neurodevelopmental impairment. FNIRS elicited indices of PFC activation during conditions of positive emotional arousal that may be useful in differentiating alcohol-related neurodevelopmental impairment. In addition to its usefulness as a potential biomarker to improve identification of children with FASD, fNIRS has the potential of being used as a tool for evaluating both psychiatric medications and behavioral interventions (Ehlis et al., 2014) to improve their habilitative care as a result of its relatively low cost and ease of use relative to other traditional neuroimaging procedures.

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Abbreviations

EF	executive functioning
HBO	oxygenated hemoglobin
HBR	deoxygenated hemoglobin
PAE	prenatal alcohol exposure
PFC	prefrontal cortex
FASDs	fetal alcohol spectrum disorders
fNIRs	functional near-infrared spectroscopy
MBLL	modified Beer-Lambert Law
ADHD	attention-deficit hyperactivity disorder
LEDS	light-emitting diodes
COBI	cognitive optical brain imaging
SMAR	sliding-window motion artifact rejection
FETCH	frustration emotion task for children

CBCL child behavior checklist
CON controls
CC clinical contrast group

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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