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The Use of Functional Near-Infrared Spectroscopy to Differentiate Alcohol-Related Neurodevelopmental Impairment

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Abstract

Oxygenated (HBO) and deoxygenated hemoglobin (HBR) levels in the prefrontal cortex (PFC) were measured using functional near-infrared spectroscopy (fNIRS) to determine if PFC activity during a cognitive inhibition task distinguishes children with prenatal alcohol exposure (PAE, n=26) from both typically-developing controls (n=19) and a contrast group of children with other neurobehavioral problems (n=14). Despite showing evidence of increased PFC activity in the non-inhibitory condition relative to controls, children in the PAE group displayed reduced PFC HBO and increased HBR relative to both other groups in the inhibitory condition, suggesting reduced PFC activity but increased oxygen consumption without sufficient oxygen replacement.

Keywords

Prenatal alcohol; fNIRS; children; FASD; executive functioning

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Authors' contributions.

JK and CC conceived of and designed the study. TEM and JH processed data for analyses. CEB and JK analyzed the results. CEB drafted the paper and all authors edited the manuscript.

Ethics approval and consent to participate.

Ethics approval was obtained from the Internal Review Board of Emory University School of Medicine (Study No.: IRB00061788).

All participants underwent an informed consent process and minors were required to provide oral or written assent for the assessments carried in the study. Participant recruitment and the study's procedures were carried out in accordance with the guidelines established by the Declaration of Helsinki.

Consent for publication.

Not applicable.

Availability of data and material.

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests.

The authors have no competing interests to declare.

BACKGROUND

The prevalence of fetal alcohol spectrum disorders (FASD) in first grade children is estimated at 1 to 5 per 100 (P. May et al., 2018), indicating that FASD is a significant public health problem. It has been proposed that the neurobehavioral outcomes of prenatal alcohol exposure (PAE) be characterized as *Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE)* with criteria being a history of more than minimal prenatal alcohol exposure and impairments in neurocognitive functioning, self-regulation, and adaptive functioning (American Psychiatric Association, 2013; Kable et al., 2016). The symptoms of neurocognitive impairment include deficits in intellectual functioning, executive functioning skills, learning, memory, and visual-spatial reasoning. One of the challenges in the validation of this proposed diagnosis is the differentiation of behavior associated with PAE from that occurring in association with other neurobehavioral disorders. As executive functioning deficits are frequently cited as being critical to many of the functional deficits commonly seen in FASD, this study evaluated whether neural activity during the performance of tasks requiring executive functioning could differentiate children with alcohol-affected neurobehavioral impairments from typically developing children and those with other diagnoses.

Executive functioning involves complex, higher-order cognitive abilities such as problem solving, planning, concept formation, set shifting, fluency, inhibition, and working memory, all of which are found to be impaired as a result of PAE (Kodituwakku, 2007; Mattson, Crocker, & Nguyen, 2011). For example, children with PAE performed poorly on a tapping inhibition task as compared to non-exposed children (Noland et al., 2003) and scored lower on measures of response inhibition, planning, and flexibility (Mattson, Goodman, Caine, Delis, & Riley, 1999). In real-world terms, parents and professionals commonly report problems with behavior control in children with PAE (Haley, Handmaker, & Lowe, 2006; Kable & Coles, 2004; Kodituwakku, Handmaker, Cutler, Weathersby, & Handmaker, 1995; Kopera-Frye, Carmichael-Olson, & Streissguth, 1997; O'Connor, 2001; O'Connor & Paley, 2009; Oosterheld & Wilson, 1997). It has been suggested that executive tasks that require goal management and the maintenance of information in working memory, along with prefrontal cortical output, may best discriminate alcohol-exposed children in need of intervention (Kodituwakku et al., 1995; Mattson et al., 2010).

The complex neuropsychological abilities known as executive functions have been linked to frontal lobe projections to subcortical regions such as the basal ganglia and thalamus (Cummings, 1993). Tasks requiring self-regulation in the form of behavioral inhibition are associated with activation of the prefrontal cortex (PFC), particularly the right inferior frontal gyrus (Aron, Robbins, & Poldrack, 2004; Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Swick, Ashley, & Turken, 2011). Consistent with this observation, a number of human studies have found that PAE impairs development, structure, function and connectivity of the PFC, suggesting a basis for observed problems with executive functioning (Malisza et al., 2012; Wozniak et al., 2013). For example, alcohol-affected individuals display hypoperfusion of blood in the left frontal region at rest (Riikonen, Salonen, Partanen, & Verho, 1999) and a reduction in serotonin transporter binding in the medial frontal cortex (Riikonen et al., 2005). Children and adolescents with PAE display

reductions in orbital-frontal lobe size, particularly in the left hemisphere, and enhancements in grey matter density in the dorsal frontal cortex (Sowell et al., 2002), both of which are regions known to be involved in executive functioning in humans.

In addition to structural and resting-state alterations in PFC activity, increasing evidence using functional magnetic resonance imaging (fMRI) suggests that PAE alters prefrontal activity during tasks requiring the use of executive functions but the pattern of the results have not been consistent. Increased PFC activity was reported in the left, medial, and right middle frontal gyri during inhibition trials of a “Go/No-Go” task (Fryer et al., 2007), in the right dorsal frontal cortex during verbal paired associate learning (Sowell et al., 2007), and in the left dorsal frontal, left inferior parietal, and bilateral posterior temporal activity as compared to typically-developing children during a Sternberg verbal working memory task (O’Hare et al., 2009). During a verbal “N-back” working memory task, only non-syndromal children with high PAE displayed enhanced dorsal PFC BOLD responses as compared to controls, whereas FASD children recruited parietal and cerebellar regions and displayed reduced activity in Broca’s area compared to controls (Diwadkar et al., 2013).

Responses to spatial working memory tasks of children with PAE have produced mixed results. Increase activity has been reported in the frontal, insular, temporal, occipital, and subcortical BOLD responses to a spatial working memory task (Spadoni et al., 2009) and in the dorsolateral PFC and parietal cortex responses in the 1-Back phase of a spatial working memory task (Malisza et al., 2012). However, in the 0-Back phase of the latter study, PAE children displayed reduced right dorsolateral and bilateral parietal activation. During a task of spatial working memory, FASD children displayed increased fMRI activity in the inferior and middle frontal lobe but showed reduced superior frontal activation. They also failed to display greater activity with increasing task difficulty as seen in controls (Malisza et al., 2005).

Additionally, reduced activity was also reported in the caudate (Fryer et al., 2007) and the left medial and posterior temporal regions (Sowell et al., 2007). FASD children displayed reduced right inferior and middle frontal gyrus, right dorsal lateral prefrontal cortex, and right parietal lobe activation in an “N-back” facial recognition task (Astley et al., 2009). While processing numbers, PAE young adults displayed lower activation in parietal and pre-frontal regions during a subtraction task (Dehaene et al., 2004) and, in another study, FASD children recruited parietal regions during number processing whereas typically developing controls showed enhanced frontal BOLD activity (Meintjes et al., 2010). Although the direction of change is not consistent across tasks, it is evident that PFC functioning is abnormal in children with PAE, displaying either impairments in activation or compensatory enhancements for potentially reduced neural efficiency (see (Coles and Li, 2011) for review).

Further study in this population may be facilitated by neuroimaging techniques that are less intimidating to young children with FASDs. Functional near infrared spectroscopy (fNIRS) is a non-invasive neuroimaging technique that uses near infrared light to detect changes in concentrations of oxygenated (HBO) and deoxygenated (HBR) hemoglobin. Due to its methodology, fNIRS is largely resistant to motion artifacts and requires minimal physical

constraints, making it well-suited for studies of children, particularly those with neurodevelopmental disabilities. Like fMRI, fNIRS relies on the hemodynamic response, in which oxygenated blood (HBO) is recruited to activated tissue, and can be used as an indirect measure of neuronal activity (Fox, Raichle, Mintun, & Dence, 1988). A net increase in HBO and decrease in HBR is associated with neural activity (Fox & Raichle, 1986), resulting from increased cerebral blood flow that is larger than the increase in oxygen consumption during neural activation.

fNIRS uses infrared light (650–1000 nm) that is emitted from a light source placed on a pad that is secured to the participant's forehead. Light penetrates human biological tissue at this wavelength and is either differentially absorbed by the primary chromophores, HBO and HBR, or diffusely scattered (Ferrari & Quaresima, 2012). Measures of light absorption are converted to changes in HBO and HBR concentrations using the Modified Beer-Lambert Law (MBLL) (Kocsis, Herman, & Eke, 2006). In different clinical populations, fNIRS has been used to assess PFC activity during executive tasks (Ayaz et al., 2012; Boecker, Buecheler, Schroeter, & Gauggel, 2007; Herrmann, Plichta, Ehli, & Fallgatter, 2005; Perlman, Luna, Hein, & Huppert, 2014), yielding results comparable to those obtained with fMRI (Amyot et al., 2012; Heinzel et al., 2013). Using fNIRS to assess alterations in hemodynamic changes in the brain, 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 two different contrast groups (Kable, Coles, & CIFASD, 2017). Increased levels of HBR in the lateral PFC areas in the absence of the corresponding reduction in HBO is suggestive of disruption to the perfusion of oxygen to the activated neural tissue (A. Villringer, 1997).

In the current study, we investigated PFC neural activity by indexing oxygenation changes during the Task of Executive Control (TEC) in children (age 6–18 yrs.) with a positive history of PAE, as well as two groups of children with no PAE, typically developing and those with other clinically significant behavioral problems. The TEC is designed to elicit cognitive inhibitory responses. Given that PAE is associated with impairments in cognitive and behavioral inhibition (Kodituwakku, 2007; Mattson et al., 2011; Mattson et al., 1999; Noland et al., 2003), we hypothesized that relative concentrations of HBO and HBR would vary among groups, reflecting alterations in PFC activity in children with PAE compared to control and contrast groups. More specifically, because the right lateral PFC previously has been associated with inhibitory processing (Aron et al., 2004; Chikazoe et al., 2007; Jourdan Moser et al., 2009; Monden et al., 2012; Monden et al., 2015; Swick et al., 2011; Xiao et al., 2012), we hypothesized alterations in this region in the PAE group. Increases in HBO and reductions in HBR would reflect increased oxygen delivery, while reductions in HBO and increased HBR would reflect reduced oxygen delivery and increased oxygen consumption. Regional alterations in PFC oxygenation that distinguish children with PAE from both other groups may be useful clinical biomarkers to identify children in need of intervention services.

METHODS

Sample:

Participants included children (6–18 years) in the Atlanta metropolitan area previously enrolled in a national multisite investigation to identify the key differentiating neurobehavioral characteristics of FASD (Mattson et al., 2013). Participants either had a clinical FASD diagnosis or were identified in the community (i.e. at local PTA events, public health fairs) when there was a confirmed positive history of PAE. Guardians underwent an informed consent procedure approved by the Human Subjects Committee of Emory University School of Medicine. Participants were compensated for each aspect of the study, including \$20 for the fNIRS assessment. Participants were excluded if they were non-fluent in English, had a history of significant head injury or loss of consciousness lasting greater than 30 minutes, were adopted from abroad after age 5 or 2 years before the assessment, displayed evidence of other known causes of intellectual deficiency (e.g., congenital hypothyroidism, chromosomal abnormalities, neurofibromatosis), or had a psychiatric or physical disability that prevented study completion.

PAE Sample (n = 31): Participants had a history of heavy prenatal alcohol exposure (>13 drinks/week or >4 drinks/occasion during pregnancy) or a clinical FAS or partial FAS diagnosis. PAE histories were obtained via retrospective maternal report or social service, legal, or medical records. In cases where accurate exposure history was unattainable, children were considered to have heavy PAE if mothers were known to be “alcoholic” or alcohol abusing during pregnancy. Children recruited from the clinic were identified by clinicians through medical records under a HIPAA partial waiver or by their families. Details regarding the FASD diagnostic procedures of the clinic are published elsewhere (Coles et al, 2016) but involved a multidisciplinary team assessment that included a physician trained in assessing alcohol-related dysmorphic features and neurodevelopmental evaluations conducted by psychologists.

Control Group Recruitment (n = 20): Typically developing non-alcohol exposed siblings of the children receiving services at the clinic and or those from the community were recruited. Participants had a reliable history of minimal (< 1 drink/week, never >2 drinks/occasion) or no exposure in pregnancy and no clinically significant emotional or behavioral concerns.

Contrast Group Recruitment (n = 20): A contrast sample of children with identified behavioral or emotional concerns were recruited from siblings of those seen in the FASD diagnostic clinic, from community recruitments, and from the waiting room of a child psychiatric clinic. Participants either had a prior mental health diagnosis or a consultation from a primary doctor or mental health professional was obtained regarding emotional or behavioral problems. Participants had a reliable history of minimal (< 1 drink/week, never >2 drinks/occasion) or no alcohol exposure in pregnancy.

fNIRS Tasks.

The Tasks of Executive Control (TEC) is a commercially available assessment program that uses standardized normative data to assess responses in a computerized sorting game (Isquith, Roth, & Gioia, 2010). The TEC incorporates different levels of working memory demand needed to identify the appropriate response, often referred to as an n-back task, and a cognitive inhibitory component often referred to as a go-no go component. The tasks involve sorting items based on certain rules into one of two boxes (Standard or Target Box) by pressing one of two keys on a standard computer keyboard marked with blue and red stickers, respectively. Items are presented for 400 ms with an inter-stimulus interval of an average of 2,000 ms. The game consists of 3 *n-back* phases (0, 1 and 2) and two inhibitory conditions (yes or no) resulting in 6 conditions. For each condition, 100 items are presented and the total duration was approximately 3 min and 25 s. Due to task difficulty for this group, and drop out in performance, we are only comparing the hemodynamic changes in the PFC during the 0-back portions of the test, where maintenance of prior trials in working memory is not required. In the non-inhibitory condition, participants must sort an image of a zebra into the Target Box by pressing the red button, and all other images into the Standard Box using the blue button (Figure 1). The inhibitory condition is similar but periodically presents stimuli (i.e. items surrounded by a grey box) where no response is required and the participant must inhibit the impulse to press one of the sorting keys. For each condition, a brief practice session is provided by the software to ensure that the child understands the sorting rules prior to administering the full stimuli for each of the conditions. To ensure that all participants were actively engaged for the duration of the task, individuals who had 90% incorrect answers were excluded from analysis. TEC software outputs standardized T-scores of performance parameters, allowing comparison across age ranges.

fNIRS Procedures.

Hemodynamic changes in the prefrontal cortex were measured using a wearable neuroimaging device (FNIR Devices, Biopac, FNIRS 100A) and Cognitive Optical Brain Imaging (COBI) Studio software (Ayaz et al., 2011). This non-invasive procedure continuously monitors blood oxygenation and volume changes associated with brain function. The system consists 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. The pad contained a reusable, flexible circuit board that contains 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. LED lights were measured continuously at 500 ms intervals at wavelengths of 730 nm and 850 nm to simultaneously estimate HBO and HBR levels. Sensors were placed with a 2.5 cm source-detector separation, which reportedly allows for approximately 1.25 cm depth penetration into the cortex (Ayaz et al., 2011). Data was collected from 16 optodes across the forehead and a 10 second baseline collected prior to initiating the task was used as a referent for estimating changes in PFC functioning during task performance. Validation studies of fNIRS and fMRI studies have been done indicating good agreement between the methods (Amyot et al., 2012; Heinzl et al., 2013). The fNIRS signals were then pre-processed using FNIRSoft@ from Drexel University (Ayaz, Izzetoglu, Shewokis, & Onaral, 2010). First, a linear phase, low pass band filter (0.1 to 0.15 Hz) was

applied to attenuate high frequency components of the signal, which eliminated physiological signals such as heart rate and respiration, and then this was followed by a median filtering procedure. Next, the Sliding-window Motion Artifact Rejection (SMAR) algorithm (Ayaz et al., 2010; Ayaz et al., 2011) was applied. Estimates of HBO and HBR were then computed from the cleaned data using the Modified Beer-Lambert Law (MBLL) (Kocsis et al., 2006) to estimate chromophore concentration from detected light intensity and a final detrending procedure was then applied to eliminate measurement errors associated with the prolonged sampling procedure. Within each condition of the TEC, only the first 180 seconds of data was used for analysis of the phasic changes in blood oxygenation across time for each of the conditions. This resulted in a total of 360 time samples of HBO and HBR values for each optode in both the non-inhibitory and inhibitory conditions. FNIRS does not measure absolute HBO and HBR concentrations and values represent changes in hemoglobin levels relative to the baseline period, which controls for within subject variation in optical absorption and refraction of the near infrared light. As a result, values of HBO and HBR may be positive or negative in value.

Statistical Analysis.

All statistical procedures were performed in SAS Studio University Edition. Descriptive statistics and frequency distributions were computed to describe participant characteristics and game performance. Averages of blood oxygenation values were taken across the left most four (lateral left), middle eight (medial), and right four (lateral right) optodes for each of the 360 time samples of HBO and HBR and used for further analyses. To examine group differences in PFC blood oxygenation, generalized linear mixed models (GLMM) were performed separately on HBO and HBR levels within each region (left, middle, right) for the inhibitory and non-inhibitory game conditions. As data displayed nonlinear trajectories across time and to account for repeated measures of the same subject, time was modeled with a cubic spline function. The GLMM models included a random intercept to account for baseline differences in oxygenation levels across groups. Fixed effects modeled were age, group and an interaction between group and splined time. Group differences at predetermined time points within the beginning (45 s), middle (90 s), and end (135 s) of the task were estimated using least square means. Within each GLMM, false discovery rate (FDR) was controlled using a Benjamini Hochberg correction with an FDR of 0.10 (Benjamini & Hochberg, 1995). Any time points not predetermined were run in *post-hoc* exploratory analyses.

RESULTS

Group Characteristics.

As thresholds for performance are often used in studies (Kodali et al, 2017; Spadoni et al., 2009) to control for participant engagement in the task, a total of 1 control, 5 PAE, and 6 contrast children were excluded for having greater than 90% incorrect responses, leaving $n = 19, 26,$ and 14 remaining in analyses, respectively. The difference in exclusion rates did not differ between groups ($\chi^2 = 4.47, p = 0.11$).

Group characteristics are provided in Table 1 for only those that were included in the final fNIR analysis. Twelve of the children with PAE were diagnosed with FAS or partial FAS and 14 meet criteria for significant levels of prenatal alcohol exposure while in utero. Groups did not differ in age, sex, race, ethnicity, or child protective services involvement. However, contrast and PAE groups had a greater percentage of participants with behavioral concerns ($\chi^2 = 29.0$, $p < 0.0001$) and developmental or learning problems ($\chi^2 = 7.7$, $p = 0.021$), which included Attention Deficit and Hyperactivity Disorder diagnoses. The groups differed in placement ($\chi^2 = 15.4$, $p = 0.004$) with 50.0% of those in the PAE group being placed with someone other than a biological parent as compared to 94.7% of controls and 92.9 % of the contrast group who were with a bioparent. Overall level of intellectual functioning as measured by the Differential Abilities Scale, 2nd Editions General Conceptual Ability score did not differ across groups.

Task Performance.

Among those remaining, TEC performance largely did not differ across groups (Table 2). A main effect of group was detected for incorrect responses in the non-inhibitory condition ($F_{2,56} = 3.64$, $p = 0.03$), with children with PAE performing more poorly than the contrast group ($p = 0.01$)).

fNIRS.

Across each of the samples collected ($n=360$) for the non-inhibitory and inhibitory tasks, incomplete data for HBO occurred for 7.75% of the left, 6.13% of the medial, and 9.50% of the right PFC. Incomplete HBR data occurred for 7.83% of the left, 6.25% of the medial, and 9.47% of the right PFC. These results are comparable to our previous research (Kable, Coles, & CIFASD, 2017) and in other samples (Perlman, et al 2014).

Graphs of mean changes in PFC hemoglobin concentration relative to a 10-s baseline period demonstrate relative differences in HBO and HBR as a function of group, inhibitory condition, and time (Figure 2, 3). Figure 2 depicts mean HBO and HBR across time, and Figure 3 depicts least square mean estimates within each group at 45, 90, and 135 s. It should be noted that all HBO and HBR values are relative to a baseline collection period before the game begins, so can be negative or positive and do not represent absolute hemoglobin concentrations. Thus, values may be referred to as HBO and HBR for simplicity in comparing group differences, but actually represent change in HBO and HBR from baseline.

Non-inhibitory condition.

Significant main effects of group were detected in left HBO ($F_{2,55} = 33.06$, $p < 0.0001$), left HBR ($F_{2,55} = 12.38$, $p < 0.0001$), medial HBO ($F_{2,55} = 9.57$, $p = 0.00027$), and medial HBR ($F_{2,55} = 4.86$, $p = 0.011$), but not right HBO ($F_{2,55} = .15$, $p = 0.87$) or right HBR ($F_{2,55} = 2.01$, $p = 0.14$). The main effect of age was not significant in any region for HBO or HBR ($p > 0.05$). Children with PAE and the contrast group displayed greater increases in HBO in the left PFC than did the control group at 45 s (PAE v Control, $p = 0.00048$; Contrast v Control, $p = 0.09$; Fig 2A, 3A). The contrast group displayed greater increases in HBO in the medial PFC than did the control group at 45 s ($p = 0.037$). Exploratory analyses of group

differences were run at 3 s for the left, medial, and right HBO values as control and contrast appeared to display an initial dip in HBO at the start of the task. In all PFC regions at 3 s, children with PAE displayed greater HBO values than did control (left, $p < 0.0001$; medial, $p < 0.0001$; right, $p = 0.011$) and contrast (left, $p < 0.0001$; medial, $p = 0.0033$; right, $p = 0.031$) groups. The contrast group also displayed greater PFC HBO than controls in the left ($p = 0.034$) and medial ($p = 0.0088$) regions, but not in the right PFC ($p = 0.86$). No least square mean differences between groups survived FDR correction for HBR in any region at any predetermined time point (Fig 2B, 3B).

Inhibitory condition.

Significant main effects of group were detected in left HBO ($F_{2, 55} = 3.43$, $p = 0.040$), left HBR ($F_{2, 55} = 5.71$, $p = 0.0056$), medial HBO ($F_{2, 55} = 31.54$, $p < 0.0001$), medial HBR ($F_{2, 55} = 16.58$, $p < 0.0001$), right HBO ($F_{2, 55} = 4.53$, $p = 0.015$), but not right HBR ($F_{2, 55} = 2.34$, $p = 0.11$). A significant main effect of age was only detected for HBR in the left PFC during the inhibitory condition, with HBR increasing with age ($F_{1, 55} = 5.15$, $p = 0.027$). PFC HBO was reduced and PFC HBR was increased in children with PAE at multiple time points relative to other groups. Children with PAE displayed reduced HBO values in the medial PFC at 45 s and 90 s compared to both control (45 s, $p = 0.012$; 90 s, $p = 0.017$) and contrast (45 s, $p = 0.017$; 90 s, $p = 0.075$) groups (Fig 2C, 3C). At 135 s, medial PFC HBO in children with PAE was only reduced relative to the contrast group ($p = 0.075$). Right PFC HBO was reduced in children with PAE relative to controls at 45 s ($p = 0.026$) and 90 s ($p = 0.021$). PFC HBR was increased in children with PAE relative to contrast children in the left PFC at 45 ($p = 0.032$) and 90 s ($p = 0.032$), and in the right PFC at 45 s ($p = 0.086$) and 90 s ($p = 0.086$), and relative to control children in the right PFC at 90 s ($p = 0.086$; Fig 2D, 3D). The contrast group also displayed reduced HBR relative to controls in the left PFC at 45 s ($p = 0.032$).

DISCUSSION

Heavy consumption of alcohol during the prenatal period disrupts neural development and alters functioning of the PFC during tasks of executive control (Kable et al., 2017; Roussotte et al., 2011). Here, PFC blood oxygenation during an executive task requiring cognitive inhibition was estimated using fNIRS in children with PAE compared to typically developing control children and those with a history of behavioral disturbances without PAE. Control, PAE, and contrast groups performed similarly on the task. However, children with PAE displayed reduced oxygen delivery, as indexed by reduced HBO, and increased deoxygenated blood (HBR) during inhibitory game phases. PAE was related to reduced increases in HBO in the medial and lateral right PFC, and higher levels of HBR in the lateral left and right PFC. Contrast children, however, displayed reduced HBR in the PFC in inhibitory phases relative to other groups, suggestive of enhanced PFC activation. The increase in HBR in children with PAE in the inhibitory condition is suggestive of increased oxygen consumption, and is accompanied by reduced HBO relative to other groups, suggestive of impaired oxygen replacement.

The lateral PFC has previously been associated with inhibitory control using fNIRS (Inoue et al., 2012; Jourdan Moser et al., 2009; Miao et al., 2017; Monden et al., 2012; Monden et al., 2015; Rodrigo et al., 2016; Xiao et al., 2012), thus impairment in this region may reflect the PFC neural mechanisms underlying executive problems associated with PAE.

Interestingly, the right lateral PFC has repeatedly been linked to inhibitory processing (Aron et al., 2004; Chikazoe et al., 2007; Jourdan Moser et al., 2009; Monden et al., 2012; Monden et al., 2015; Swick et al., 2011; Xiao et al., 2012) and reduced levels of HBO in this area differentiated the PAE group from controls, suggesting reduced neural activation in children with PAE during cognitive inhibition may be a method of differentiating children impacted by PAE from typically developing children. Previous research in children with ADHD has pointed to lateral PFC hypoactivation as reflected by a reduction in HBO while performing tasks of cognitive inhibition (ex. Go/NoGo), and fNIRS is being pursued as a diagnostic tool for this developmental disorder (Inoue et al., 2012; Jourdan Moser et al., 2009; Miao et al., 2017; Monden et al., 2012; Monden et al., 2015; Xiao et al., 2012).

The medial PFC, which is linked to reward processing (J. May et al., 2004) and self-monitoring (Davidson, Fox, & Kalin, 2007; Devinsky, Morrell, & Vogt, 1995), displayed reduced HBO in children with PAE relative to both other groups (Graham, Glass, & Mattson, 2016; Nguyen et al., 2014; Rai et al., 2016; Zimmerberg & Riley, 1988), suggesting that reduced neural activation in the medial area during cognitive inhibition may be helpful in differentiating children impacted by PAE from both typically developing children and those with other clinical conditions not caused by PAE.

In non-inhibitory phases, control and contrast children displayed an initial depletion of oxygenated blood (HBO) reflective of increased oxygen consumption before oxygenated blood is recruited to the area, an effect known as an initial dip (Buxton, 2001). This was particularly apparent in the left PFC, a region important for dealing with negative emotions (Perlman et al., 2014) and planning (Ruocco et al., 2014). The initial depletion of HBO was not seen in children with PAE, suggesting a disruption to initiation of neural activation. Thus, children with PAE displayed increased HBO levels at the beginning of the task relative to both other groups.

In the inhibitory condition, the PAE group displayed reduced medial and lateral right PFC HBO and increased lateral left and right PFC HBR relative to both other groups, suggesting reductions in neuronal activity. Children with PAE also displayed less deviation from baseline HBO and HBR levels than did other groups, perhaps suggesting impaired oxygen transport. Reductions in PFC activity and impairments in oxygen transport in the inhibitory component may underlie problems with attention and concentration seen in children with PAE (Koditwakku, 2007; Mattson et al., 2011).

Additionally, the contrast group displayed reduced HBR in the left PFC relative to controls, which is reflective of a compensatory enhancement in PFC activity. This pattern has previously been detected in non-alcohol exposed children with Attention Deficit Hyperactivity Disorder using fNIRS (Jourdan Moser et al., 2009). Children with ADHD displayed increased oxygen consumption and brain activation in the right dorsolateral PFC while performing the Stroop task of cognitive inhibition. However, the majority of fNIRS

studies of children with ADHD have revealed PFC hypoactivation during cognitive inhibition tasks (Inoue et al., 2012; Jourdan Moser et al., 2009; Miao et al., 2017; Monden et al., 2012; Monden et al., 2015; Xiao et al., 2012), although HBR levels are rarely reported. Further studies including multiple clinical groups and reporting HBO/HBR dynamics may help to distinguish features of the hemodynamic response in children with PAE from other clinical diagnoses.

Comparison to fMRI in PAE

During the task requiring inhibition, children with PAE displayed reduced HBO and increased HBR levels compared to other groups, suggesting reduced PFC activity. Reductions in PFC BOLD signals have previously been associated with PAE during number processing (Meintjes et al., 2010), facial recognition (Astley et al., 2009), subtraction (Dehaene et al., 2004), and working memory tasks (Diwadkar et al., 2013; Malisza et al., 2005). Additionally, PAE-induced impairments may lead to the recruitment of brain networks not typically associated with a given executive task (Diwadkar et al., 2013). During cognitive inhibition, children with PAE display increased medial and superior fMRI responses, but reduced responses in the inferior PFC and anterior cingulate relative to controls (Fryer et al., 2007; Kodali et al., 2017). However, increased anterior cingulate and frontal BOLD responses during inhibition have also been reported (O'Brien et al., 2013; Ware et al., 2015). As fNIRS has poor spatial resolution, it is unknown whether the reduction in HBO and increase in HBR are specific to particular PFC sub-regions. However, it is possible that reductions occurred in the inferior PFC, a region previously associated with cognitive inhibition (Aron et al., 2004; Chikazoe et al., 2007; Swick et al., 2011). Furthermore, increased HBO was observed in the PAE and contrast groups during the start of non-inhibitory trials relative to controls, which would similarly be reflected as an increased BOLD response in an fMRI paradigm. However, this difference was actually due to an initial depletion of oxygenated blood in controls, which is reflective of an initial enhancement in neural activity.

Results may not be consistent across imaging modalities due to differences in hemodynamic measurements. Whereas fNIRS measures HBR and HBO levels separately, the BOLD signal in fMRI is a single readout of the ratio of HBO to HBR. BOLD levels are primarily dependent on the amount of deoxygenated hemoglobin, as HBR is paramagnetic and degrades the magnetic signal (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). However, the dynamics between HBO and HBR levels cannot be meaningfully discerned from fMRI investigations. Typically, a net increase in HBO and a decrease in HBR is viewed as increased oxygenated blood flow to an activated brain region (Cutini, Moro, & Bisconti, 2012). However, increased oxygen usage, and thus increased neural activity, could be reflected in increased HBR and constant or reduced HBO, a phenomenon occurring immediately after stimulus onset (Buxton, 2001). Furthermore, if only HBO increases, and HBR remains the same, the activation would not be reflected in the BOLD signal (H. Obrig & Villringer, 2003), thus fNIRS may be more sensitive to oxygenation changes in certain instances. However, fNIRS is only able to measure superficial layers of the cerebral cortex directly underlying the skull, and it is not as able to access deeper, subcortical brain structures as is fMRI (Ferrari & Quaresima, 2012; H. Obrig & Villringer, 1995). Thus the joint use of

fNIRS and fMRI can help to tease apart spatial and neurophysiology dynamics underlying brain activation.

Limitations

Although fNIRS has many advantages, including obtaining estimates of both levels HBO and HBR, portability, and resistance to motion artifact, limitations in the ability to make inferences about neural activity from oxygenation levels must be considered. Blood volume in both arteries and veins, cerebral blood flow, and oxygen usage all affect the interpretation of HBR and HBO levels (Buxton, 2001). Furthermore, noise in the signal originates from motion artifacts and interference from blood pressure, respiration and cardiac pulsation (Boas et al., 2001), although statistical procedures are used to account for these artifacts (Lloyd-Fox, Blasi, & Elwell, 2010; Tak & Ye, 2014). Additionally, poor spatial resolution with fNIRS prohibits the precise investigation of PFC sub-regions. Skin pigmentation and skull thickness also contribute to variability in measurements between individuals. Finally, extracranial blood flow may contribute to observed changes in oxygenation, however the contribution is likely minor as changes in hemoglobin as measured by fNIRS correlate with cerebral blood flow measurements using positron emission tomography (K. Villringer et al., 1997).

Although the 0-Back inhibitory condition evokes cognitive inhibitory control, an aspect of executive functioning, group comparisons of the conditions that required greater working memory demand were not able to be used. Group comparisons of the hemodynamic changes in the 1-Back and 2-Back conditions were sampled in this study but poor performance levels in the clinical groups (PAE and Contrast) created a confound, making it difficult to make conclusions regarding whether differences in the hemodynamic changes in the brain were the result of the child not appropriately engaging in the task or the result of alterations in vascular functioning and/or hemodynamic processes. Alternative tasks that integrate higher levels of working memory demand and inhibitory vs. non-inhibitory may be needed in future studies or limiting the lower range of ability level of the clinical contrast groups may be used to reduce the differential performance.

Within the 0-Back condition, poor performance was not associated with participant age. The age range of excluded individuals was 6–14 yrs (specifically, 6, 6, 7, 7, 7, 7, 8, 10, 11, 12, 12, 14) and varied by group status with the clinical groups (PAE and Contrast) having the highest rates of excluded individuals (Control = 1 eliminated; 10 yrs, PAE = 5 eliminated; 6, 7, 12, 12, 14 yrs, and Contrast = 6 eliminated; 6, 7, 7, 7, 8, 11 yrs.), suggesting that poor performance was the result of the common neurobehavioral deficits seen in these groups.

This study did not make an attempt to control for shared variability associated with siblings that may have impacted the results. This is in part because the definition of siblings in this study is not uniform as siblings may have been biological siblings, foster-siblings, half-siblings and adopted siblings. In addition, there was variability in the child's experience of the family environment with some children being adopted very early in development and others were relatively new to the current family environment. Caregivers in the study also varied from biological parents, grandparents, legal guardians, and foster parents. These familial factors may have contributed to error variance and may have impacted our

comparisons of group differences. Unfortunately, with the limited sample size in this study, it would not be possible to statistically evaluate all of the potential factors that may influenced the outcomes. In future research, a larger sample may help with controlling for the various family and environmental experiences that may contribute to these group differences.

Oxygen transport in FASD

Although we are using fNIRS as a proxy to understand neural activity in the forebrain, it is possible that changes in oxygenation are a direct reflection of alterations in vasculature resulting from PAE. Children with FASDs display increases in cardiac malformations and heart murmurs (Jones, Jones, & Del Campo, 2013). However, the neurovascular connections between the heart and brain and the impact on neural oxygen perfusion in FASD are largely unstudied. Interestingly, PAE impacts blood vasculature in the placenta and increases oxidative stress in the fetus (Ramadoss & Magness, 2012). In mice, PAE reduces cortical vascular density, promotes microvessel death, inhibits radial orientation of microvessels, and alters the expression of vascular endothelial growth factor receptors in the cerebral cortex (Jegou et al., 2012). Similarly, impairments in radial organization of the vasculature in the neocortex and alterations in brain vessel area are observed in postmortem PAE fetal brain tissue (Jegou et al., 2012; Solonskii, Logvinov, & Kutepova, 2008). Ethanol also leads to micro-hemorrhages primarily in the cortex of rats exposed during the equivalent of the human third-trimester (Welch, Mayfield, Leibowitz, Baculis, & Valenzuela, 2016). Risk for brain hemorrhage is also high in premature babies reportedly exposed to high levels of ethanol (Holzman, Paneth, Little, & Pintomartin, 1995). Thus, it is important for future studies to explore disruptions in vasculature and resulting impairments on oxygen transport and diffusion in children with PAE.

CONCLUSIONS

Oxygen utilization and transport differed in children with PAE as a function of inhibitory requirements. During a task of cognitive inhibition, children with PAE displayed reduced PFC activation. These results suggest that oxygen utilization is altered in children with PAE during tasks requiring attention and cognitive inhibition and these alterations differentiate children with PAE from other clinical conditions. Future studies are required to investigate whether functional alterations in PFC oxygenation associate with behavioral measures of executive function and real-world behavioral deficits, with the aim of using fNIRS as a tool in diagnosis and evaluation of intervention programs for children with FASDs. Because of the ease, portability, and cost of fNIRS, it may provide a useful diagnostic tool for PAE-related neurodevelopmental impairments in order to guide appropriate treatment or intervention strategies unique to alcohol-induced pathology.

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List of Abbreviations.

PAE	Prenatal alcohol exposure
FASDs	Fetal Alcohol Spectrum Disorders
FAS	Fetal Alcohol Syndrome
fNIRS	functional near infrared spectroscopy
HBO	oxygenated hemoglobin
HBR	deoxygenated hemoglobin
TEC	Task of Executive Control

REFERENCES.

- American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
- Amyot F, Zimmermann T, Riley J, Kainerstorfer JM, Chernomordik V, Mooshagian E, . . . Wassermann EM (2012). Normative database of judgment of complexity task with functional near infrared spectroscopy--application for TBI. *Neuroimage*, 60(2), 879–883. doi:10.1016/j.neuroimage.2012.01.104 [PubMed: 22306800]
- Aron AR, Robbins TW, & Poldrack RA (2004). Inhibition and the right inferior frontal cortex. *Trends Cogn Sci*, 8(4), 170–177. doi:10.1016/j.tics.2004.02.010 [PubMed: 15050513]
- Astley SJ, Aylward EH, Olson HC, Kerns K, Brooks A, Coggins TE, . . . Richards T (2009). Functional magnetic resonance imaging outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. *J Neurodev Disord*, 1(1), 61–80. doi:10.1007/s11689-009-9004-0 [PubMed: 21547622]
- Ayaz H, Izzetoglu M, Shewokis PA, & Onaral B (2010). Sliding-window motion artifact rejection for Functional Near-Infrared Spectroscopy. *Conf Proc IEEE Eng Med Biol Soc*, 2010, 6567–6570. doi: 10.1109/IEMBS.2010.5627113
- Ayaz H, Shewokis PA, Bunce S, Izzetoglu K, Willems B, & Onaral B (2012). Optical brain monitoring for operator training and mental workload assessment. *Neuroimage*, 59(1), 36–47. doi:10.1016/j.neuroimage.2011.06.023 [PubMed: 21722738]
- Ayaz H, Shewokis PA, Curtin A, Izzetoglu M, Izzetoglu K, & Onaral B (2011). Using MazeSuite and functional near infrared spectroscopy to study learning in spatial navigation. *J Vis Exp*(56). doi: 10.3791/3443
- Benjamini Y, & Hochberg Y (1995). Controlling the False Discovery Rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society B*, 57(1), 289–300.
- Boas DA, Brooks DH, Miller EL, DiMarzio CA, Kilmer M, Gaudette RJ, & Zhang Q (2001). Imaging the body with diffuse optical tomography. *Ieee Signal Processing Magazine*, 18(6), 57–75. doi:Doi 10.1109/79.962278
- Boecker M, Buecheler MM, Schroeter ML, & Gauggel S (2007). Prefrontal brain activation during stop-signal response inhibition: an event-related functional near-infrared spectroscopy study. *Behavioural Brain Research*, 176(2), 259–266. doi:10.1016/j.bbr.2006.10.009 [PubMed: 17112604]

- Buxton RB (2001). The elusive initial dip. *Neuroimage*, 13(6 Pt 1), 953–958. doi:10.1006/nimg.2001.0814 [PubMed: 11352601]
- Chikazoe J, Konishi S, Asari T, Jimura K, & Miyashita Y (2007). Activation of right inferior frontal gyrus during response inhibition across response modalities. *J Cogn Neurosci*, 19(1), 69–80. doi:10.1162/jocn.2007.19.1.69 [PubMed: 17214564]
- Coles CD, Gailey AR, Mulle JG, Kable JA, Lynch ME, & Jones KL (2016). A Comparison Among 5 Methods for the Clinical Diagnosis of Fetal Alcohol Spectrum Disorders. *Alcohol Clin Exp Res*. doi:10.1111/acer.13032
- Coles CD, & Li Z (2011). Functional neuroimaging in the examination of effects of prenatal alcohol exposure. *Neuropsychol Rev*, 21(2), 119–132. doi:10.1007/s11065-011-9165-y [PubMed: 21484401]
- Cummings JL (1993). Frontal-subcortical circuits and human behavior. *Arch Neurol*, 50(8), 873–880. [PubMed: 8352676]
- Cutini S, Moro SB, & Bisconti S (2012). Functional near infrared optical imaging in cognitive neuroscience: an introductory review. *Journal of near Infrared Spectroscopy*, 20(1), 75–92. doi:10.1255/jnirs.969
- Davidson RJ, Fox A, & Kalin NH (2007). Neural bases of emotion regulation in nonhuman primates and humans In Gross JJ (Ed.), *Handbook of Emotion Regulation* (pp. 47–68). New York: The Guilford Press.
- Dehaene S, Molko N, Cohen L, & Wilson AJ (2004). Arithmetic and the brain. *Curr Opin Neurobiol*, 14(2), 218–224. doi:10.1016/j.conb.2004.03.008 [PubMed: 15082328]
- Devinsky O, Morrell MJ, & Vogt BA (1995). Contributions of anterior cingulate cortex to behaviour. *Brain*, 118 (Pt 1), 279–306. [PubMed: 7895011]
- Diwadkar VA, Meintjes EM, Goradia D, Dodge NC, Warton C, Molteno CD, . . . Jacobson JL (2013). Differences in cortico-striatal-cerebellar activation during working memory in syndromal and nonsyndromal children with prenatal alcohol exposure. *Hum Brain Mapp*, 34(8), 1931–1945. doi:10.1002/hbm.22042 [PubMed: 22451272]
- Elliot CD (2007). *Differential Ability Scales*, Second Edition. San Antonio, TX: PsychCorp.
- Ferrari M, & Quaresima V (2012). A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. *Neuroimage*, 63(2), 921–935. doi:10.1016/j.neuroimage.2012.03.049 [PubMed: 22510258]
- Fox PT, & Raichle ME (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci U S A*, 83(4), 1140–1144. [PubMed: 3485282]
- Fox PT, Raichle ME, Mintun MA, & Dence C (1988). Nonoxidative glucose consumption during focal physiologic neural activity. *Science*, 241(4864), 462–464. [PubMed: 3260686]
- Fryer SL, Tapert SF, Mattson SN, Paulus MP, Spadoni AD, & Riley EP (2007). Prenatal alcohol exposure affects frontal-striatal BOLD response during inhibitory control. *Alcohol Clin Exp Res*, 31(8), 1415–1424. doi:10.1111/j.1530-0277.2007.00443.x [PubMed: 17559542]
- Graham DM, Glass L, & Mattson SN (2016). The Influence of Extrinsic Reinforcement on Children with Heavy Prenatal Alcohol Exposure. *Alcohol Clin Exp Res*, 40(2), 348–358. doi:10.1111/acer.12959 [PubMed: 26842253]
- Haley DW, Handmaker NS, & Lowe J (2006). Infant stress reactivity and prenatal alcohol exposure. *Alcohol Clin Exp Res*, 30(12), 2055–2064. doi:ACER251 [pii] 10.1111/j.1530-0277.2006.00251.x [PubMed: 17117971]
- Heinzel S, Haeussinger FB, Hahn T, Ehli AC, Plichta MM, & Fallgatter AJ (2013). Variability of (functional) hemodynamics as measured with simultaneous fNIRS and fMRI during intertemporal choice. *Neuroimage*, 71, 125–134. doi:10.1016/j.neuroimage.2012.12.074 [PubMed: 23313421]
- Herrmann MJ, Plichta MM, Ehli AC, & Fallgatter AJ (2005). Optical topography during a Go-NoGo task assessed with multi-channel near-infrared spectroscopy. *Behavioural Brain Research*, 160(1), 135–140. doi:10.1016/j.bbr.2004.11.032 [PubMed: 15836908]
- Holzman C, Paneth N, Little R, & Pintomartin J (1995). Perinatal Brain Injury in Premature-Infants Born to Mothers Using Alcohol in Pregnancy. *Pediatrics*, 95(1), 66–73. [PubMed: 7770312]

- Inoue Y, Sakihara K, Gunji A, Ozawa H, Kimiya S, Shinoda H, et al. (2012). "Reduced prefrontal hemodynamic response in children with ADHD during the Go/NoGo task: a NIRS study." *Neuroreport*, 23(2): 55–60. [PubMed: 22146580]
- Isquith PK, Roth RM, & Gioia GA (2010). *Tasks of Executive Control: Professional Manual*. Lutz, FL: PAR.
- Jegou S, El Ghazi F, de Lendeu PK, Marret S, Laudenbach V, Uguen A, . . . Gonzalez BJ (2012). Prenatal alcohol exposure affects vasculature development in the neonatal brain. *Ann Neurol*, 72(6), 952–960. doi:10.1002/ana.23699 [PubMed: 23280843]
- Jones KL, Jones MC, & Del Campo M (2013). *Smith's Recognizable Patterns of Human Malformation* (7th Edition ed.). Philadelphia, PA: Elsevier.
- Jourdan Moser S, Cutini S, Weber P, & Schroeter ML (2009). Right prefrontal brain activation due to Stroop interference is altered in attention-deficit hyperactivity disorder - A functional near-infrared spectroscopy study. *Psychiatry Res*, 173(3), 190–195. doi:10.1016/j.psychres.2008.10.003 [PubMed: 19664910]
- Kable JA, & Coles CD (2004). The impact of prenatal alcohol exposure on neurophysiological encoding of environmental events at six months. *Alcohol Clin Exp Res*, 28(3), 489–496. doi: 00000374-200403000-00016 [pii] [PubMed: 15084907]
- Kable JA, Coles CD, & Cifas. (2017). Prefrontal cortical responses in children with prenatal alcohol-related neurodevelopmental impairment: A functional near-infrared spectroscopy study. *Clin Neurophysiol*, 128(11), 2099–2109. doi:10.1016/j.clinph.2017.08.009 [PubMed: 28914230]
- Kable JA, O'Connor MJ, Olson HC, Paley B, Mattson SN, Anderson SM, & Riley EP (2016). Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE): Proposed DSM-5 Diagnosis. *Child Psychiatry Hum Dev*, 47(2), 335–346. doi:10.1007/s10578-015-0566-7 [PubMed: 26202432]
- Kocsis L, Herman P, & Eke A (2006). The modified Beer-Lambert law revisited. *Phys Med Biol*, 51(5), N91–98. doi:10.1088/0031-9155/51/5/N02 [PubMed: 16481677]
- Kodali VN, Jacobson JL, Lindinger NM, Dodge NC, Molteno CD, Meintjes EM, & Jacobson SW (2017). Differential Recruitment of Brain Regions During Response Inhibition in Children Prenatally Exposed to Alcohol. *Alcohol Clin Exp Res*, 41(2), 334–344. doi:10.1111/acer.13307 [PubMed: 28075019]
- Koditwakku PW (2007). Defining the behavioral phenotype in children with fetal alcohol spectrum disorders: a review. *Neurosci Biobehav Rev*, 31(2), 192–201. doi:10.1016/j.neubiorev.2006.06.020 [PubMed: 16930704]
- Koditwakku PW, Handmaker NS, Cutler SK, Weathersby EK, & Handmaker SD (1995). Specific impairments in self-regulation in children exposed to alcohol prenatally. *Alcohol Clin Exp Res*, 19(6), 1558–1564. [PubMed: 8749827]
- Kopera-Frye K, Carmichael-Olson H, & Streissguth AP (1997). Teratogenic effects of alcohol on attention In Burack JA & Enns JT (Eds.), *Attention, Development and Psychopathology* (pp. 171–204). New York, NY: The Guildford Press.
- Lloyd-Fox S, Blasi A, & Elwell CE (2010). Illuminating the developing brain: The past, present and future of functional near infrared spectroscopy. *Neuroscience and Biobehavioral Reviews*, 34(3), 269–284. doi:10.1016/j.neubiorev.2009.07.008 [PubMed: 19632270]
- Logothetis NK, Pauls J, Augath M, Trinath T, & Oeltermann A (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, 412(6843), 150–157. doi:10.1038/35084005 [PubMed: 11449264]
- Malisza KL, Allman AA, Shiloff D, Jakobson L, Longstaffe S, & Chudley AE (2005). Evaluation of spatial working memory function in children and adults with fetal alcohol spectrum disorders: a functional magnetic resonance imaging study. *Pediatr Res*, 58(6), 1150–1157. doi:10.1203/01.pdr.0000185479.92484.a1 [PubMed: 16306185]
- Malisza KL, Buss JL, Bolster RB, de Gervai PD, Woods-Frohlich L, Summers R, . . . Longstaffe S (2012). Comparison of spatial working memory in children with prenatal alcohol exposure and those diagnosed with ADHD: A functional magnetic resonance imaging study. *J Neurodev Disord*, 4(1), 12. doi:10.1186/1866-1955-4-12 [PubMed: 22958510]

- Mattson SN, Crocker N, & Nguyen TT (2011). Fetal alcohol spectrum disorders: neuropsychological and behavioral features. *Neuropsychol Rev*, 21(2), 81–101. doi:10.1007/s11065-011-9167-9 [PubMed: 21503685]
- Mattson SN, Goodman AM, Caine C, Delis DC, & Riley EP (1999). Executive functioning in children with heavy prenatal alcohol exposure. *Alcohol Clin Exp Res*, 23(11), 1808–1815. [PubMed: 10591598]
- Mattson SN, Roesch SC, Fagerlund A, Autti-Ramo I, Jones KL, May P, . . . Collaborative Initiative on Fetal Alcohol Spectrum, D. (2010). Toward a neurobehavioral profile of fetal alcohol spectrum disorders. *Alcohol Clin Exp Res*, 34(9), 1640–1650. doi:10.1111/j.1530-0277.2010.01250.x [PubMed: 20569243]
- Mattson SN, Roesch SC, Glass L, Deweese BN, Coles CD, Kable JA, . . . Cifas. (2013). Further Development of a Neurobehavioral Profile of Fetal Alcohol Spectrum Disorders. *Alcoholism-Clinical and Experimental Research*, 37(3), 517–528. doi:10.1111/j.1530-0277.2012.01952.x
- May J, Delgado MR, Dahl RE, Stenger VA, Ryan ND, Fiez JA, & Carter CS (2004). Event-related functional magnetic resonance imaging of reward-related brain circuitry in children and adolescents. *Biol Psychiatry*, 55(4), 359–366. doi:10.1016/j.biopsych.2003.11.008 [PubMed: 14960288]
- May P, Chambers C, Kalberg W, Zelnner J, Feldman H, Buckley D, . . . Hoyme HE (2018). Prevalence of Fetal Alcohol Spectrum Disorders in 4 US Communities *JAMA*, 319(5), 474–482. [PubMed: 29411031]
- Meintjes EM, Jacobson JL, Molteno CD, Gatenby JC, Warton C, Cannistraci CJ, . . . Jacobson SW (2010). An fMRI study of number processing in children with fetal alcohol syndrome. *Alcohol Clin Exp Res*, 34(8), 1450–1464. doi:10.1111/j.1530-0277.2010.01230.x [PubMed: 20528824]
- Miao S, Han J, Gu Y, Wang X, Song W, Li D, et al. (2017). “Reduced Prefrontal Cortex Activation in Children with Attention-Deficit/Hyperactivity Disorder during Go/No-Go Task: A Functional Near-Infrared Spectroscopy Study.” *Front Neurosci*, 11: 367. [PubMed: 28701914]
- Monden Y, Dan H, Nagashima M, Dan I, Tsuzuki D, Kyutoku Y, et al. (2012). “Right prefrontal activation as a neuro-functional biomarker for monitoring acute effects of methylphenidate in ADHD children: An fNIRS study.” *Neuroimage Clin*, 1(1): 131–140. [PubMed: 24179746]
- Monden Y, Dan I, Nagashima M, Dan H, Uga M, Ikeda T, et al. (2015). “Individual classification of ADHD children by right prefrontal hemodynamic responses during a go/no-go task as assessed by fNIRS.” *Neuroimage Clin*, 9: 1–12. [PubMed: 26266096]
- Nguyen TT, Glass L, Coles CD, Kable JA, May PA, Kalberg WO, . . . Cifas. (2014). The clinical utility and specificity of parent report of executive function among children with prenatal alcohol exposure. *J Int Neuropsychol Soc*, 20(7), 704–716. doi:10.1017/S1355617714000599 [PubMed: 25033032]
- Noland JS, Singer LT, Arendt RE, Minnes S, Short EJ, & Bearer CF (2003). Executive functioning in preschool-age children prenatally exposed to alcohol, cocaine, and marijuana. *Alcohol Clin Exp Res*, 27(4), 647–656. doi:10.1097/01.ALC.0000060525.10536.F6 [PubMed: 12711927]
- O’Brien JW, Norman AL, Fryer SL, Tapert SF, Paulus MP, Jones KL, . . . Mattson SN (2013). Effect of Predictive Cuing on Response Inhibition in Children with Heavy Prenatal Alcohol Exposure. *Alcoholism-Clinical and Experimental Research*, 37(4), 644–654. doi:10.1111/acer.12017
- O’Connor MJ (2001). Prenatal alcohol exposure and infant negative affect as precursors of depressive features in children. *Infant Mental Health Journal*, 22(3), 291–299.
- O’Connor MJ, & Paley B (2009). Psychiatric conditions associated with prenatal alcohol exposure. *Dev Disabil Res Rev*, 15(3), 225–234. doi:10.1002/ddrr.74 [PubMed: 19731386]
- O’Hare ED, Lu LH, Houston SM, Bookheimer SY, Mattson SN, O’Connor MJ, & Sowell ER (2009). Altered frontal-parietal functioning during verbal working memory in children and adolescents with heavy prenatal alcohol exposure. *Hum Brain Mapp*, 30(10), 3200–3208. doi:10.1002/hbm.20741 [PubMed: 19263420]
- Obbigg H, & Villringer A (1995). Near-infrared spectroscopy in functional activation studies: Can NIRS demonstrate cortical activation? Paper presented at the International symposium on optical imaging and metabolism, Berlin, Germany.

- Obrig H, & Villringer A (2003). Beyond the visible--imaging the human brain with light. *J Cereb Blood Flow Metab*, 23(1), 1–18. doi:10.1097/01.WCB.0000043472.45775.29
- Oosterheld JR, & Wilson A (1997). ADHD and FAS. *J Am Acad Child Adolesc Psychiatry*, 36(9), 1163. doi:S0890-8567(09)62637-X [pii] 10.1097/00004583-199709000-00004
- Perlman SB, Luna B, Hein TC, & Huppert TJ (2014). fNIRS evidence of prefrontal regulation of frustration in early childhood. *Neuroimage*, 85 Pt 1, 326–334. doi:10.1016/j.neuroimage.2013.04.057 [PubMed: 23624495]
- Rai JK, Abecassis M, Casey JE, Flaro L, Erdodi LA, & Roth RM (2016). Parent rating of executive function in fetal alcohol spectrum disorder: A review of the literature and new data on Aboriginal Canadian children. *Child Neuropsychol*, 1–20. doi:10.1080/09297049.2016.1191628
- Ramadoss J, & Magness RR (2012). Vascular effects of maternal alcohol consumption. *Am J Physiol Heart Circ Physiol*, 303(4), H414–421. doi:10.1152/ajpheart.00127.2012 [PubMed: 22730388]
- Riikonen RS, Nokelainen P, Valkonen K, Kolehmainen AI, Kumpulainen KI, Kononen M, . . . Kuikka JT (2005). Deep serotonergic and dopaminergic structures in fetal alcoholic syndrome: a study with nor-beta-CIT-single-photon emission computed tomography and magnetic resonance imaging volumetry. *Biol Psychiatry*, 57(12), 1565–1572. doi:10.1016/j.biopsych.2005.01.029 [PubMed: 15953494]
- Riikonen RS, Salonen I, Partanen K, & Verho S (1999). Brain perfusion SPECT and MRI in foetal alcohol syndrome. *Dev Med Child Neurol*, 41(10), 652–659. [PubMed: 10587040]
- Rodrigo AH, Di Domenico SI, Graves B, Lam J, Ayaz H, Bagby RM, & Ruocco AC (2016). Linking trait-based phenotypes to prefrontal cortex activation during inhibitory control. *Soc Cogn Affect Neurosci*, 11(1), 55–65. doi:10.1093/scan/nsv091 [PubMed: 26163672]
- Roussotte FF, Bramen JE, Nunez SC, Quandt LC, Smith L, O'Connor MJ, . . . Sowell ER (2011). Abnormal brain activation during working memory in children with prenatal exposure to drugs of abuse: The effects of methamphetamine, alcohol, and polydrug exposure. *Neuroimage*, 54(4), 3067–3075. doi:10.1016/j.neuroimage.2010.10.072 [PubMed: 21040792]
- Ruocco AC, Rodrigo AH, Lam J, Di Domenico SI, Graves B, & Ayaz H (2014). A problem-solving task specialized for functional neuroimaging: validation of the Scarborough adaptation of the Tower of London (S-TOL) using near-infrared spectroscopy. *Front Hum Neurosci*, 8, 185. doi:10.3389/fnhum.2014.00185 [PubMed: 24734017]
- Solonskii AV, Logvinov SV, & Kutepova NA (2008). Development of brain vessels in human embryos and fetuses in conditions of prenatal exposure to alcohol. *Neurosci Behav Physiol*, 38(4), 373–376. doi:10.1007/s11055-008-0053-8 [PubMed: 18401729]
- Sowell ER, Lu LH, O'Hare ED, McCourt ST, Mattson SN, O'Connor MJ, & Bookheimer SY (2007). Functional magnetic resonance imaging of verbal learning in children with heavy prenatal alcohol exposure. *Neuroreport*, 18(7), 635–639. doi:10.1097/WNR.0b013e3280bad8dc [PubMed: 17426589]
- Sowell ER, Thompson PM, Mattson SN, Tessner KD, Jernigan TL, Riley EP, & Toga AW (2002). Regional brain shape abnormalities persist into adolescence after heavy prenatal alcohol exposure. *Cereb Cortex*, 12(8), 856–865. [PubMed: 12122034]
- Spadoni AD, Bazinet AD, Fryer SL, Tapert SF, Mattson SN, & Riley EP (2009). BOLD response during spatial working memory in youth with heavy prenatal alcohol exposure. *Alcohol Clin Exp Res*, 33(12), 2067–2076. doi:10.1111/j.1530-0277.2009.01046.x [PubMed: 19740135]
- Swick D, Ashley V, & Turken U (2011). Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *Neuroimage*, 56(3), 1655–1665. doi:10.1016/j.neuroimage.2011.02.070 [PubMed: 21376819]
- Tak S, & Ye JC (2014). Statistical analysis of fNIRS data: a comprehensive review. *Neuroimage*, 85 Pt 1, 72–91. doi:10.1016/j.neuroimage.2013.06.016 [PubMed: 23774396]
- Villringer A (1997). Functional neuroimaging optical approaches In Villringer A. a. D., U (Ed.), *Optical Imaging of Brain Function and Metabolism 2* (Vol. *Advances in Experimental Medicine and Biology*, pp. 1–25). New York: Plenum Press.
- Villringer K, Minoshima S, Hock C, Obrig H, Ziegler S, Dirnagl U, . . . Villringer A (1997). Assessment of local brain activation In Villringer A & Dirnagl U (Eds.), *Advances in*

Experimental Medicine and Biology: Optical Imaging of Brain Function and Metabolism 2 New York: Plenum Press.

- Ware AL, Infante MA, O'Brien JW, Tapert SF, Jones KL, Riley EP, & Mattson SN (2015). An fMRI study of behavioral response inhibition in adolescents with and without histories of heavy prenatal alcohol exposure. *Behavioural Brain Research*, 278, 137–146. doi:10.1016/j.bbr.2014.09.037 [PubMed: 25281280]
- Welch JH, Mayfield JJ, Leibowitz AL, Baculis BC, & Valenzuela CF (2016). Third trimester-equivalent ethanol exposure causes micro-hemorrhages in the rat brain. *Neuroscience*, 324, 107–118. doi:10.1016/j.neuroscience.2016.03.004 [PubMed: 26964687]
- Wozniak JR, Mueller BA, Bell CJ, Muetzel RL, Hoecker HL, Boys CJ, & Lim KO (2013). Global functional connectivity abnormalities in children with fetal alcohol spectrum disorders. *Alcohol Clin Exp Res*, 37(5), 748–756. doi:10.1111/acer.12024 [PubMed: 23240997]
- Xiao T, Xiao Z, Ke X, Hong S, Yang H, Su Y, et al. (2012). "Response inhibition impairment in high functioning autism and attention deficit hyperactivity disorder: evidence from near-infrared spectroscopy data." *PLoS One*, 7(10): e46569. [PubMed: 23056348]
- Zimmerberg B, & Riley EP (1988). Prenatal alcohol exposure alters behavioral laterality of adult offspring in rats. *Alcohol Clin Exp Res*, 12(2), 259–263. [PubMed: 3287990]

Figure 1. Task design.

The first two blocks of the Tasks of Executive Control (TEC) program are depicted. In the non-inhibitory condition, participants sort an image of a zebra in to the Target Box by pressing the red button, and all other images into the Standard Box using the blue button. During the inhibitory condition, participants must inhibit the impulse to press one of the sorting keys when items are surrounded by a box. For each condition, 100 items are presented and the total duration was approximately 3 min and 25 s. Actual test items are not displayed. Icons are by Lee Mette from thenounproject.com.

Figure 2. Oxygenation changes across time.

Changes in HBO (red) and HBR (blue) over time within each region in the non-inhibitory (A,B) and inhibitory (C,D) conditions are displayed. Children with PAE displayed greater HBO than other groups in the left and medial PFC during non-inhibitory game play. Children with PAE displayed reduced HBO in the medial and right PFC, and increased left and right PFC HBR relative to other groups during the inhibitory game condition. Least square mean and standard error (shaded areas) estimates from GLMM are displayed. Asterisks indicate areas with significant group differences in least square mean estimates after FDR correction (see Figure 2). α indicates significant exploratory analyses where children with PAE displayed greater HBO than other groups.

Figure 3. Group differences in oxygenation.

Graphs represent average regional changes from baseline in HBO and HBR in the noninhibitory (A,B) and inhibitory (C,D) conditions at predetermined time points. Children with PAE displayed reduced HBO and increased HBR during the inhibitory game condition. Least square means and standard error estimates from GLMM are displayed. Asterisks indicate areas with significant group differences in least square mean estimates after FDR correction.

Table 1.

Sample demographics by group status.

Measure	Controls (n=19)	Prenatal Alcohol-Exposed (n=26)	Contrast (n=14)	Statistic, p-Value
Child's Age [M (SD); min-max]	11.2 (3.0;6-16)	10.7 (2.9;6-16)	10.8 (3.1;6-18)	ns
Child's Sex [n (% male)]	8 (42.1)	12 (46.2)	7 (50.0)	ns
Race [n (% African American or Mixed Race with African American)]	18 (94.7)	22 (84.6)	13 (92.9)	ns
Ethnicity [n (% Non-Hispanic)]	19 (100)	21 (80.8)	12 (85.7)	ns
Parental Behavioral Concern [n (% yes)]	2 (10.5)	18 (69.2)	14 (100)	$\chi^2=29.0, p < .0000$
Developmental or Learning Problem [n (% yes)]	1 (5.3)	10 (38.5)	2 (14.3)	$\chi^2=7.7, p = .021$
Child Protective Service Involvement [n (% yes)]	5 (26.3)	10 (38.5)	1 (7.1)	ns
Placement				$\chi^2=15.4, p = .004$
Biological Parent [n (% yes)]	18 (94.7)	13 (50.0)	13 (92.9)	
Kinship Care [n (% yes)]	0 (0)	5 (19.2)	1 (7.1)	
Legal Guardian/Adoptive Parent [n (% yes)]	1 (5.3)	8 (30.8)	0 (0)	
DAS GCA ¹ [M (SD)]	89.5 (11.7)	84.8 (12.6)	81.3 (8.0)	ns

¹DAS GCA, Differential Abilities Scale General Conceptual Ability Score (Elliot, 2007).

Table 2.

Performance on the Task of Executive Control (TEC).

Measure	Controls (n=19)	Prenatal Alcohol-Exposed (n=26)	Contrast (n=14)	Statistic, p-Value
<i>Non-Inhibitory Condition</i>				
Incorrect	46.63 (1.13)	49.88 (1.49)	44.07 (1.87)	$F_{2,56}=3.64$, $p=0.03$
Target Response Time	48.95 (2.18)	49.85 (1.94)	47.93 (1.59)	ns
Standard Response Time	49.32 (2.37)	47.19 (1.41)	47.07 (1.13)	ns
<i>Inhibitory Condition</i>				
Incorrect	45.32 (2.03)	49.50 (1.48)	43.71 (2.03)	ns
Target Response Time	50.74 (2.71)	46.76 (1.92)	45.86 (1.85)	ns
Standard Response Time	52.68 (3.26)	49.56 (2.25)	46.57 (1.52)	ns

Mean, standard errors, and analysis of variance of resulting T-scores on the TEC are displayed. Children with PAE performed worse than contrast children in the Non-Inhibitory Condition ($p=0.01$), but no other differences were detected.