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Prefrontal cortical responses in children with prenatal alcohol-related neurodevelopmental impairment: A functional near-infrared spectroscopy study

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HIGHLIGHTS

- PFC activity, using fNIRS, discriminated prenatally alcohol-exposed (PAE) children.
- Children with PAE had reduced activation in the medial PFC areas.
- Children with PAE had greater oxygen depletion in all areas of PFC.

ABSTRACT

Objective: Disruption in the neural activation of the prefrontal cortex (PFC) in modulating arousal was explored in children with heavy prenatal alcohol exposure (PAE), who have known neurobehavioral impairment.
Methods: During a task that elicits frustration, functional near-infrared spectroscopy (fNIRS) was used to measure PFC activation, specifically levels of oxygenated (HBO) and deoxygenated (HBR) hemoglobin, in children with PAE (n = 18) relative to typically developing Controls (n = 12) and a Clinical Contrast group with other neurodevelopmental or behavioral problems (n = 14).
Results: 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 sampled relative to both other groups. Children in the Control group demonstrated greater differentiation of PFC activity than did children with PAE. Children in the Clinical Contrast group demonstrated the greatest differences in PFC activity between valences of task conditions.
Conclusions: Specific patterns of PFC activation differentiated children with PAE from typically developing children and children with other clinical problems.
Significance: FNIRS assessments of PFC activity provide new insights regarding the mechanisms of commonly seen neurobehavioral dysfunction in children with PAE.

1. Introduction

Fetal Alcohol Spectrum Disorders (FASDS) is a term that refers to a cluster of physical and neurobehavioral abnormalities, including facial dysmorphology, growth retardation, and disruption to brain development, that have been investigated for over four decades in human and animal model studies of prenatal alcohol exposure (PAE) (Riley et al., 2011). Although public health awareness and prevention efforts have increased as a result of these findings, recent estimates of the prevalence of Fetal Alcohol Syndrome (FAS), the most severe FASD condition, have ranged from 0.6 to 0.9 percent of live births with the full range of FASDs estimated to fall between 2.4 and 4.8 percent (May et al., 2014). Despite the fairly high prevalence rates, most children with FASDs are misdiagnosed (Chasnoff et al., 2015). Improved methods of identifying alcohol-affected children are needed, including the development of biomarkers of the neural damage caused by PAE.

Although much attention was initially devoted to understanding the deficits in general cognitive functioning associated with a

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history of PAE (Mattson et al., 1997), many individuals who are exposed do not meet criteria for an intellectual disability (Mattson and Riley, 1998) but still demonstrate a complex array of neurobehavioral problems (Kable et al., 2016). Among the most significant problems are the persistent and wide-ranging difficulties in a set of cognitive skills known as executive functions (EF), particularly in planning, organization, and problem-solving (Mattson et al., 1999; Kodituwakku et al., 2001, 2006; Schonfeld et al., 2006; Vaurio et al., 2008; Green et al., 2009; Mattson et al., 2010). Evidence from the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) neurobehavioral study of children, 8–17 years, indicated that assessment of executive functioning differentiated individuals with FASD from other clinical groups (i.e. ADHD) (Mattson et al., 2013).

EF problems are expressed in multiple ways in everyday functioning of children with FASD. Difficulties with incorporating environmental feedback to correct a response are suggested by deficits in overall performance on progressive planning tasks (Kodituwakku et al., 1995; Green et al., 2009) and by more repetition errors on learning tasks (McGee et al., 2008). Making shifts in cognitive sets while learning has also been found to be impaired in individuals with PAE, specifically reversal shifts (Coles et al., 1997; Green et al., 2009; Chasnoff et al., 2010). Impairments in verbal fluency (Kodituwakku et al., 2006; Vaurio et al., 2008) and working memory skills (Rasmussen, 2005; Rasmussen et al., 2011) have also been reported. Children with PAE have been found to have problems in sustaining attention and the appropriate mental effort (Brown et al., 1991; Kodituwakku et al., 2006; Aragon et al., 2008) needed to complete tasks while inhibiting impulses (Herman et al., 1980; Streissguth et al., 1986, 1993, 1994; Kodituwakku et al., 2006). Finally, behavioral and emotional control problems are commonly reported by caregivers of children with FASDs (Kodituwakku et al., 1995; Kopera-Frye et al., 1997; Oesterheld and Wilson, 1997; O'Connor, 2001; Kable and Coles, 2004; Haley et al., 2006; O'Connor and Paley, 2009).

Evidence suggests that the prefrontal cortex (PFC) (Malisza et al., 2005; Fryer et al., 2007; Sowell et al., 2007; Burke et al., 2009; O'Hare et al., 2009; Zhou et al., 2011) and the connectivity of the PFC to other brain regions (Wozniak et al., 2013) is adversely impacted by PAE and may be the neural substrate from which the deficits in EF skills arise. Frontal lobe deficits are thought to underlie difficulties with response inhibition, poor behavioral regulation, and other EF skill deficits noted in alcohol-exposed individuals (Niccols, 2007). Further, deficits in both EF and social functioning have been related to the metabolic composition of the frontal lobes (Nash et al., 2006), leading many to theorize that disruption to PFC activity may also help to explain impairments in interpersonal relationships and social skills commonly seen among individuals affected by PAE (Thomas et al., 1998; McGee and Riley, 2006; Schonfeld et al., 2006, 2009).

Evidence suggests identification of EF skills (Mattson et al., 2010) and PFC activity that supports these skills may be effective in diagnosing individuals affected by PAE and in need of intervention services. An alternative to traditional neuroimaging methods (functional magnetic resonance imaging (fMRI) and positron emission tomography (PET)) is functional near-infrared spectroscopy (fNIRS), which has been used to assess local hemodynamic changes in PFC activity (Ferrari and Quaresima, 2012; Boas et al., 2014) and has the advantage of reducing movement-artifact errors and anxiety, particularly in younger children, related to the equipment used with traditional neuroimaging assessments. The fNIRS technology has advanced so that the equipment used is now portable, noninvasive, and commercially available at relatively low cost when compared to fMRI and PET scanning equipment (Ferrari and Quaresima, 2012; Boas et al., 2014).

FNIRS assesses levels of oxygenated (HBO) and deoxygenated (HBR) hemoglobin by emitting infrared light, ranging from 650 to 1000 uv, through human biologic tissue, which is nearly transparent to light in this range (Ferrari and Quaresima, 2012; Scholkmann et al., 2014). The infrared light is then differentially absorbed by chromophores, which are light-absorbing molecules (specifically, HBO or HBR), or diffusely scattered by other human tissue. 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 and using the modified Beer-Lambert Law (MBLL) (Kocsis et al., 2006) to make adjustments needed for diffusion of the light through human tissue. The placement of the sensors directly on the scalp minimizes the impact of movement artifacts often found in other neuroimaging techniques. This method has been validated by documenting changes in blood oxygenation levels relative to blood oxygenation levels obtained in fMRI (Amyot et al., 2012; Heinzel et al., 2013) and PET studies (Obrig and Villringer, 1995). Changes in brain activation levels using fNIRS have been found to differentiate known clinical groups from typically developing children (Ishii-Takahashi et al., 2014; Wiley and Riccio, 2014) and to be related to parent-reported measures of behavioral functioning (Perlman et al., 2014). Changes in activation obtained from fNIRS have already been used to assess the impact of pharmacological interventions for children with Attention Deficit-Hyperactivity Disorder (ADHD) (Oner et al., 2011; Schecklmann et al., 2011; Monden et al., 2012; Matsuura et al., 2014; Araki et al., 2015) but have not yet been applied to understanding individual differences in children with FASDs.

To evaluate prenatal alcohol-related differences in PFC activity as measured by fNIRS, we used three groups of children: (1) children with a history of PAE (PAE), (2) typically developing children without a history of PAE (Controls), and (3) children with clinically significant developmental, learning, or behavioral problems (Clinical Contrast) who do not have a history of PAE. PFC activity was assessed during a task designed to elicit arousal and the associated PFC inhibitory responses needed to modulate the arousal during the course of the task. Indices of PFC activity (levels of oxygenated (HBO) and deoxygenated hemoglobin (HBR)) were anticipated to vary as a function of group status.

2. Methods

2.1. Participants

Children who had enrolled in a larger multisite collaborative project designed to identify neurobehavioral characteristics that differentiate children with FASD from other groups of children (Mattson et al., 2013) were recruited for this study. Participants were from the Atlanta metropolitan area who agreed to undergo neurobehavioral testing, a physical exam and allowed a 3-D photograph of their face to be obtained for the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) study. After being pre-screened for enrollment criteria, guardians were asked to sign an informed consent form for the various components of the study, including a separate consenting procedure for the fNIRS assessment. Consenting procedures and documents were approved by the Human Subjects Committee of the Emory University School of Medicine. Financial incentives were given to participants for each aspect of the multisite study assessment procedures, including a $20 reimbursement for participation in the fNIRS assessment. Exclusionary criteria for the CIFASD neurobehavioral study included being non-fluent in English, having a history of traumatic head injury or a loss of consciousness lasting over 30 min, being adopted from abroad after 5 years of age or within 2 years before enrollment, having other known causes of abnormal brain