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Two-year cortical trajectories are abnormal in children and adolescents with prenatal alcohol exposure

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ABSTRACT

Objectives: Cortical abnormalities in prenatal alcohol exposure (PAE) are known, including in gyrification (LGI), thickness (CT), volume (CV), and surface area (CS). This study provides longitudinal and developmental context to the PAE cortical development literature.

Experimental design: Included: 58 children with PAE and 52 controls, ages 6–17 at enrollment, from four Collaborative Initiative on FASD (CIFASD) sites. Participants underwent a formal evaluation of physical anomalies and dysmorphic facial features associated with PAE. MRI data were collected on three platforms (Siemens, GE, and Philips) at four sites. Scans were spaced two years apart. Change in LGI, CT, CS, and CV were examined.

Principal observations: Several significant regional age-by-diagnosis linear and quadratic interaction effects in LGI, CT, and CV were found, indicating atypical developmental trajectories in PAE. No significant correlations were observed between cortical measures and IQ.

Conclusions: Regional differences were seen longitudinally in CT, CV, and LGI in those with PAE. The findings represent important insights into developmental trajectories and may have implications for the timing of assessments and interventions in this population. It is noteworthy that cortical metrics did not correlate with IQ, suggesting that more specific aspects of cognitive development may need to be explored to provide further context.

1. Introduction

Fetal Alcohol Spectrum Disorders (FASD) is a clinical umbrella term encapsulating fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol-related neurodevelopment disorder (ARND), and alcohol-related birth defects (ARBD); all of which are caused by prenatal alcohol exposure (PAE). The effects of PAE include observable abnormalities such as facial dysmorphology, growth deficiency, and neurodevelopmental disruption, leading to serious impact on quality of life. Neuroimaging has helped highlight the neurodevelopmental effects, reliably demonstrating both macrostructural and microstructural brain abnormalities (Archibald et al., 2001; Nardelli et al., 2011; Roussotte et al., 2012; Sowell et al., 2008, 2002; Swayze et al., 1997; Wozniak et al., 2009) for reviews, see (Lebel et al., 2011; Moore et al., 2014). More subtle disruptions in functional connectivity have also been observed (Roussotte et al., 2011; Santhanam et al., 2011; Wozniak et al., 2013, 2011) and a few studies have begun to show atypical cortical development including abnormal gyrification (De Guio et al., 2014; Hendrickson et al., 2017; Infante et al., 2015), cortical thickness (Fernández-Jaén et al., 2011; Robertson et al., 2016; Sowell et al., 2008; Treit et al., 2014; Yang et al., 2012; Zhou et al., 2011), and cortical surface area and volume (Lebel et al., 2012; Leigland et al., 2013; Migliorini et al., 2015; Rajaprakash et al., 2014; Roussotte et al., 2012; Treit et al., 2013).

Much of what is known about cortical development in PAE has come from cross-sectional studies. Longitudinal studies have the potential to

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illustrate patterns of disrupted development that may not always be apparent in a cross-sectional "snapshot". The existing small literature on longitudinal cortical development in PAE suggests differences in cortical volume trajectories between individuals with PAE and controls in posterior brain regions, particularly in parietal cortex (Lebel et al., 2012). Atypical longitudinal cortical thinning has also been observed in children and adolescents with PAE, especially within medial frontal and parietal brain regions (Treit et al., 2014).

The current study sought to add to this literature with a two-year longitudinal examination of change across multiple metrics of cortical development as part of the Collaborative Initiative on FASD (CIFASD) multi-site study. We applied methods that have not previously been used in this context, including longitudinal analyses of cortical change at the vertex-wise level. Probing for differences at this level has the potential to reveal patterns not previously seen using larger regions of interest (ROIs).

The purpose of the study, therefore, was to test for potential differences in developmental trajectories in children and adolescents with PAE compared to controls to better characterize the long-term neurodevelopment "cascades" that are initiated by early insults to the brain in PAE. In addition, we also sought to examine relationships between important clinical characteristics (such as diagnostic characteristics and cognitive functioning) and cortical development, knowing that cognition is tied closely to cortical development in PAE (Dubois et al., 2008; Hendrickson et al., 2017; Shaw et al., 2006). Lastly, we sought to use this multi-site project to evaluate the robustness of structural cortical measures across multiple clinical samples evaluated on different MRI scanners.

2. Methods

2.1. Participants

Participants were enrolled in the study as part of CIFASD. Details about the CIFASD project are available in a separate publication (Mattson et al., 2010) and at www.cifasd.org. For the current study, participants were recruited from four CIFASD sites (University of Minnesota, University of Southern California/Children's Hospital of Los Angeles, San Diego State University, and Emory University School of Medicine) and scanned between 2012 and 2014. Follow-up scans took place between 2014 and 2017 approximately 2 years after the initial scan. Prenatal alcohol exposure histories were obtained through retrospective maternal report, social service, legal, and medical records. Participants were included in the PAE group if there was a history of heavy PAE (> 13 drinks/week or > 4 drinks per occasion at least once per week during pregnancy) or when such exposure was suspected in a child with a FAS diagnosis based on dysmorphology. In some cases, detailed history about exposure amounts was unattainable and decisions about inclusion or exclusion were made on the available evidence. For example, PAE was inferred if the mother was known to have had alcoholism and had contact with the police or social services during the pregnancy. In all cases, alcohol was the predominant substance of abuse. Participants were included in the non-exposed control group if there was a reliable history of minimal (< 1 drink/week, never > 2 drinks on any one occasion) or no reported exposure during pregnancy.

Control participants were recruited with flyers, mailings to control participants of previous non-CIFASD studies, online advertisements, and referrals from participants with PAE. Advertisements and flyers were placed in neighborhoods and online locations chosen to maximize the ethnic, racial, and socioeconomic diversity of the control participants so as to best match the participants with PAE. Control participants were screened by telephone, as were participants with PAE.

Participants (PAE and controls) were evaluated using a standardized examination conducted by a member of the CIFASD Dysmorphology Core (KLJ) who had not previously met the child and was not told the child's status (PAE or control). The dysmorphologist made a determination of FAS based on two or more of the following key facial features: thin vermillion border, smooth philtrum, and short palpebral fissure length − together with either microcephaly (occipital-frontal circumference ≤10%ile) or growth deficiency (height or weight ≤10% ile) or both.

Additional exclusion criteria for all subjects included another developmental disorder (ex. Autism), very low birthweight (< 1500 g), traumatic brain injury (including head injury with loss of consciousness > 2 min), other medical condition affecting the brain (ex. Epilepsy), severe psychiatric disability that would prevent participation (ex. psychosis or mania), substance use by the participant, English as a second language, international adoption after age 5, or contraindications to MRI scanning.

Control participants were excluded for parent-reported history of prenatal substance exposure (other than tobacco and caffeine exposure) and for diagnosed psychiatric conditions. Parents or caregivers of all participants were administered the Diagnostic Interview Schedule for Children-IV (C-DISC-IV; (Shaffer et al., 2000)). Because pre-screening was utilized during recruitment, very few enrolled control participants had any psychiatric symptoms. The C-DISC-IV data revealed the following: 1 control had ADHD symptoms, 3 had Oppositional Defiant symptoms, 2 had Conduct Disorder symptoms, none had depressive symptoms; none had anxiety symptoms. Psychiatric co-morbidity was not an exclusion criterion for participants with PAE because it is well-recognized that co-morbidity is a common feature of FASD (Streissguth and O'Malley, 2000). Based on the C-DISC-IV data, 31 participants in the PAE group had ADHD symptoms, 19 had Oppositional Defiant symptoms, 8 had Conduct Disorder symptoms, 2 had anxiety symptoms, and 3 had depressive symptoms.

Participants were ages 6–17 at the time of the first MRI scan. The majority of participants completed the neurocognitive evaluation and MRI on the same day. In a few cases, they were separated by a few days or weeks. A total of 110 participants (58 with PAE & 52 Controls) met inclusion criteria, had baseline and follow up scans, and were included in this analysis. Table 1 contains the demographics for the participants who were included in the analyses after eliminating those with excessive movement and aberrant image processing (see Results section for complete description).

All participants underwent an Institutional Review Board (IRB)-approved informed consent process involving a parent or guardian as well as a separate assent process with the child. All study procedures were approved by the IRBs at each of the four sites. Participants were compensated for their time.

2.2. Evaluations

Neuropsychological testing was conducted during one or (occasionally) two sessions by trained research assistants who were blind to participant group. Quality control methods included a video review of test administration procedures and a detailed scoring check for every 10th administration. From a larger battery of neuropsychological measures administered in CIFASD, only IQ is examined here (Differential Ability Scales − Second Edition (DAS-II) (Elliott, 2007)). Demographic and historical data were acquired on all CIFASD participants. Substance exposure histories, racial and ethnic background, and socioeconomic status (SES) via the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975) are examined here. These data are contained in Table 1 and/or Results Section 3.1.

2.3. MRI acquisition procedure

MRI data were acquired at four sites on scanners from three vendors: Children's Hospital of Los Angeles (Philips Achieva); University of California – San Diego (General Electric MR750); University of Minnesota and Emory University (both Siemens Tim Trio). The acquisition sequence was modeled after protocols developed for multi-site