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# Cortical gyrification is abnormal in children with prenatal alcohol exposure

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ABSTRACT

*Objectives:* Prenatal alcohol exposure (PAE) adversely affects early brain development. Previous studies have shown a wide range of structural and functional abnormalities in children and adolescents with PAE. The current study adds to the existing literature specifically on cortical development by examining cortical gyrification in a large sample of children with PAE compared to controls. Relationships between cortical development and intellectual functioning are also examined.

*Experimental design:* Included were 92 children with PAE and 83 controls ages 9–16 from four sites in the Collaborative Initiative on FASD (CIFASD). All PAE participants had documented heavy PAE. All underwent a formal evaluation of physical anomalies and dysmorphic facial features. MRI data were collected using modified matched protocols on three platforms (Siemens, GE, and Philips). Cortical gyrification was examined using a semi-automated procedure.

*Principal observations:* Whole brain group comparisons using Monte Carlo z-simulation for multiple comparisons showed significantly lower cortical gyrification across a large proportion of the cerebral cortex amongst PAE compared to controls. Whole brain comparisons and ROI based analyses showed strong positive correlations between cortical gyrification and IQ (i.e. less developed cortex was associated with lower IQ).

*Conclusions:* Abnormalities in cortical development were seen across the brain in children with PAE compared to controls. Cortical gyrification and IQ were strongly correlated, suggesting that examining mechanisms by which alcohol disrupts cortical formation may yield clinically relevant insights and potential directions for early intervention.

## 1. Introduction

Prenatal alcohol exposure (PAE) can cause a range of abnormalities including facial dysmorphology, growth deficiency, microcephaly, brain alterations, and neurocognitive deficits (reduced IQ scores, executive functioning impairments, etc.). Clinically, the effects of PAE manifest along a range of outcomes commonly referred to as fetal alcohol spectrum disorders (FASD). Although facial dysmorphology and growth deficiency represent overt exposure-related outcomes, subtle brain alterations and neurodevelopmental delays are a less-apparent but devastating set of outcomes. Neuroimaging has made significant contributions to research in FASD, particularly in regard to brain function and structure. Recently, several studies have demonstrated functional connectivity disruptions in PAE, (Roussotte et al., 2011; Santhanam et al., 2011; Wozniak et al., 2013, 2011). A larger body of work has shown a range of structural brain abnormalities (Archibald et al., 2001; Jones et al., 2010; Nardelli et al., 2011; Roussotte et al., 2012; Sowell et al., 2002; Swayze et al., 1997); for reviews, see (Lebel et al., 2011; Moore et al., 2014).

Only recently has it become feasible to examine complex cortical structure in detail using MRI. Recently, a study examining young children showed a significant reduction in cortical folding (cortical gyrification) amongst participants with PAE compared to healthy controls (De Guio et al., 2014). Abnormalities in cortical development were seen in several regions of interest (ROI) and broadly across the brain in measures that included sulcal index, sulcal depth, and fold opening. A second study examining cortical gyrification in adolescents with PAE showed reduced cortical folding in PAE compared to matched

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controls (Infante et al., 2015). In this study, the differences were seen primarily in the bilateral insula and bilateral visual cortices on the both the medial and lateral aspects of the occipital lobe. Studies examining related measures of cortical development, such as cortical surface area, have also found evidence for altered development in those with PAE (Alcohol Related Neurodevelopment Disorder in this case) compared to controls (Rajaprakash et al., 2014).

The current study sought to add to the existing literature by generating a large sample size from the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) multi-site study. We hypothesized that this larger sample size and correspondent increase in statistical power might reveal more widespread abnormalities in cortical structure than previous smaller studies - primarily because analyses of this type necessitate multiple comparison corrections in order to conduct ROI or vertex-wise analyses. We also sought to test the robustness of cortical gyrification measurements across multiple samples on different MRI scanners.

Because a number of processes that are critical to cortical development and gyrification occur during early to mid-gestation, we expected that PAE would be associated with significant abnormalities in cortical structure when examined during childhood and adolescence. We hypothesized that cortices would be smoother (less mature) in those with PAE compared to controls and that abnormalities in gyrification would be associated with lower global cognitive functioning. The advent of new tools that facilitate quantification of cortical gyrification using standard MRI images and semi-automated processing streams will ultimately allow investigators to ask important questions about relationships between early insults to cortical development and cognition in populations with neurodevelopmental disorders such as FASD.

## 2. Methods

### 2.1. Participants

Participants were enrolled in the study as part of CIFASD, a multi-site investigation of brain, neurocognitive, and physical developmental anomalies in FASD. Detailed information about the CIFASD project is 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 (Los Angeles, San Diego, Minneapolis, and Atlanta) between 2012 and 2014. PAE histories were obtained through retrospective maternal report or social service, legal, or medical records. Control participants were recruited with flyers, mailings to control participants of previous non-CIFASD studies, online advertisements, and referrals from participants with FASD. 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 FASD. Control participants were screened by telephone, as were participants with FASD.

Participants were included in the PAE group if there was a history of heavy PAE (> 13 drinks/week or > 4 drinks on any one occasion during pregnancy) or when such exposure was suspected in a child with an FAS diagnosis. In some cases, detailed history about exposure amounts or patterns of exposure was unattainable and decisions about inclusion or exclusion were made on the available evidence. Children were considered to have heavy PAE if mothers were known to have alcoholism or were known to abuse alcohol during 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 exposure during pregnancy.

Participants (PAE and controls) were evaluated using a standardized examination conducted by a member of the CIFASD Dysmorphology Core (KLJ) who was blinded to group. Based on criteria outlined previously (Jones et al., 2006; Mattson et al., 2010), the evaluation resulted in a determination of 1) Fetal Alcohol Syndrome (FAS); 2) non-FAS; or 3) a "deferred" status due to some criteria being met, but not enough to diagnose FAS. The CIFASD approach to diagnosis does not include partial-FAS or Alcohol Related Neurodevelopmental Disorder (ARND). FAS was diagnosed on the basis of 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%) or growth deficiency (height or weight ≤ 10%) or both. The deferred status was applied when an individual had A.) one key dysmorphic facial feature as described above or B.) microcephaly and growth deficiency, or C.) microcephaly or growth deficiency plus one additional minor non-facial physical malformation (railroad track ear, hockey stick palmar crease, etc.). A significant number of individuals without PAE (i.e. controls) received a "deferred" classification – highlighting the fact that the presence of one dysmorphic feature is relatively common and not diagnostic in and of itself (Jones et al., 2010).

Exclusion criteria for all subjects included another developmental disorder, very low birthweight (< 1500 g), other medical condition affecting the brain (e.g. Epilepsy), severe psychiatric disability that would prevent participation (e.g. psychosis or mania), substance use by the participant, English as a second language, international adoption after age 5, or contraindications to MRI scanning. Traumatic brain injury (including head injury with brief loss of consciousness) was treated as an exclusion criterion. No participant had a loss of consciousness > 2 min. Participants were not excluded for autistic symptoms because these are common in individuals with FASD (Aronson et al., 1997; Nanson, 1992; Stevens et al., 2013), but those who met diagnostic criteria for an autism-spectrum disorder were excluded.

Control participants were excluded for parent-reported history of PAE and for diagnosed psychiatric conditions. Parents or caregivers of all enrolled participants were administered the Diagnostic Interview Schedule for Children-IV (C-DISC-IV; (Shaffer et al., 2000)). Because the study applied pre-enrollment telephone screening for psychiatric disorders, the C-DISC-IV data for enrolled participants revealed only minimal parent-reported symptoms in the control group (2 had ADHD symptoms, 7 had Oppositional Defiant symptoms, 4 had Conduct Disorder symptoms, and one had depressive symptoms; no controls had anxiety disorder symptoms or other major psychiatric symptoms).

Psychiatric co-morbidity was not an exclusion criterion for participants with PAE because it is well-recognized that co-morbidity is an extremely common feature of FASD (Streissguth and O'Malley, 2000). Based on the C-DISC-IV data, 62 participants in the PAE group had ADHD symptoms, 40 had Oppositional Defiant symptoms, 15 had Conduct Disorder symptoms, 8 had anxiety disorder symptoms, and 4 had depressive disorder symptoms.

Participants were ages 9–16 at the time of MRI scanning. The vast 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 175 participants (92 with PAE & 83 Controls) met inclusion criteria. Table 1 contains the demographics for the participants who were included in the analyses after eliminating those with excessive movement and aberrant processing. A total of 7 participants were excluded from the analysis due to aberrant FreeSurfer processing, mostly due to the effects of excessive motion during scanning. The excluded participants were as follows: 5 male PAE (1 from Atlanta, 2 from Minnesota, 2 from San Diego), 1 male Control (Minnesota), and 1 female Control (San Diego) (see Results Section 3.2 for a more 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.

**Table 1**
Demographic characteristics of participants included in analyses.

| | PAE | Control | Statistical test |
|---|---|---|---|
| Age [M(SD,n)] | 13.09 (2.07, 92) | 13.99 (1.96, 83) | $t(173) = -2.93$, $p < 0.01$ |
| IQ [M(SD, n)] | 89.58 (12.38, 92) | 103.63 (16.63, 83) | $t(173) = -6.38$, $p < 0.001$ |
| SES [M(SD, n)] | 46.70 (12.46, 77) | 44.58 (12.05, 79) | $t(156) = -1.09$, $p = 0.28$ |
| PDSA [M(SD, n)] | 2.42 (0.78, 65) | 2.82 (0.74, 57) | $t(121) = -2.94$, $p < 0.01$ |
| Sex [n (%Female)] | 39 (42%) | 44 (53%) | $\chi^2 = 1.97$, $p = 0.16$ |
| Race | | | |
| [n(%American Indian/ Alaska Native)] | 1 (1%) | 1 (1%) | $\chi^2 = 0.0092$, $p = 0.92$ |
| [n(%Asian)] | 1 (1%) | 6 (7%) | $\chi^2 = 4.28$, $p < 0.05$ |
| [n(%Native Hawaiian or other Pacific Islander)] | 1 (1%) | 1 (1%) | $\chi^2 = 0.0054$, $p = 0.94$ |
| [n(%Black or African American)] | 27 (29%) | 26 (31%) | $\chi^2 = 0.081$, $p = 0.77$ |
| [n(%White)] | 59 (64%) | 44 (53%) | $\chi^2 = 2.23$, $p = 0.14$ |
| Ethnicity [n(%Hispanic)] | 13 (14%) | 16 (19%) | $\chi^2 = 2.49$, $p = 0.29$ |
| Handedness [n(%Right)] | 82 (89%) | 71 (86%) | $\chi^2 = 1.39$, $p = 0.71$ |
| Total intracranial volume $cm^3$[M(SD, n)] | 1364 (205, 92) | 1413 (236, 83) | $t(173) = -1.46$, $p = 0.15$ |
| Fetal alcohol syndrome diagnosis [n (%)] | | | $\chi^2 = 23.61$, $p < 0.0001$ |
| Yes | 11 (12%) | 0 | |
| No | 28 (30%) | 47 (57%) | |
| Deferred | 44 (51%) | 25 (30%) | |
| Unknown | 6 (7%) | 11 (13%) | |
| Physical manifestations | | | |
| [a]Growth deficiency | 16 (17%) | 8 (10%) | $\chi^2 = 3.73$, $p = 0.15$ |
| [b]Microcephaly[n (%)] | 15 (16%) | 0 (0%) | $\chi^2 = 15.50$, $p < 0.001$ |
| [c]Dysmorphic face [n (%)] | 33 (36%) | 12 (14%) | $\chi^2 = 10.83$, $p < 0.01$ |
| Site [n (%)] | | | $\chi^2 = 3.36$, $p = 0.34$ |
| Atlanta | 14 (15%) | 17 (20%) | |
| Los Angeles | 25 (27%) | 22 (27%) | |
| San Diego | 24 (26%) | 13 (16%) | |
| Minnesota | 29 (31%) | 31 (37%) | |

Note: Demographics are from the 175 participants included in the analyses. Age range for inclusion in the analyses was from 9 to 16 years Participants were excluded from this analysis if any examination or other assessment data were not collected. Of the initial eligible pool of 183 participants, 5 participants were eliminated for excessive motion during MRI, 2 participants (1 with AE, and 1 control) were eliminated due to failed FreeSurfer processing.
AE = Alcohol Exposure group.
SES = Socioeconomic Status; via the Hollingshead Score (if two caretakers take average).
PDSA = Puberty Development Scale Average.
FAS = Fetal Alcohol Syndrome.
ARND = Alcohol-Related Neurodevelopmental Disorder.
ARBD = Alcohol-Related Brain Damage.
[a] Height or weight ≤ 10%ile.
[b] Head circumference ≤ 10%ile.
[c] At least two of the following: Palpebral fissure length ≤ 10%ile, thin vermillion border, smooth philtrum (4 or 5 on lipometer scale).

### 2.2. Evaluations

Neuropsychological testing was conducted during one or 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, Puberty Development Scale (Petersen et al., 1988), racial and ethnic background, and socioeconomic status (SES), measure by the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975) are examined here. These data are contained in Table 1.

### 2.3. MRI acquisition procedures

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). Acquisition sequences were modeled on protocols developed for multi-site imaging by the Pediatric Imaging Neurocognition and Genetics (PING) group (Table 2) (http://ping.chd.ucsd.edu). The sequence included high resolution $T_1$-weighted images, a $T_2$-weighted set, 30-direction DTI, and gradient-echo EPI scans for resting-state fMRI. The acquisition parameters in Table 2 are just those for data examined in the current set of analyses ($T_1$). Participants were not sedated for the MRI scan nor were their usual medications modified.

### 2.4. MRI processing

#### 2.4.1. $T_1$ cortical parcellation.

Cortical parcellation of the $T_1$ volume was performed using FreeSurfer version 5.3.0 (surfer.nmr.mgh.harvard.edu) (Dale et al., 1999). Processing included removal of non-brain tissue, automated Talairach transformation, segmentation, intensity normalization, tessellation of the gray matter/white matter boundary, topology correction, and surface deformation. Data were visually inspected by a trained operator to ensure accuracy. In the case of significantly aberrant FreeSurfer processing (typically caused by motion artifact), participant data were not manually edited but, instead, the data were excluded from the analyses.

#### 2.4.2. Local gyrification index

The Local Gyrification Index (LGI) is a validated add-on metric to FreeSurfer (Schaer et al., 2008). Briefly, a smoothed outer brain surface map that does not follow the convexities of the cortex is first defined by FreeSurfer. A second map of the pial surface closely follows the folds of the cortex. Overlapping 25 mm circular regions of interest (ROIs) are then defined on the smoothed outer surface map. These ROIs are then paired with matching 25 mm pial surface ROIs. LGI is computed at each vertex as the ratio of “buried” cortex to the smoothed outer surface

**Table 2**
MRI sequence and parameters.

| Platform | Sequence | Imaging parameters | Purpose |
|---|---|---|---|
| Phillips (Los Angeles) | T1-weighted MPRAGE | TR = 6.8 ms, TE = 3.2 ms, TI = 845 ms, 170 slices, voxel size = 1x1x1.2 mm, FOV = 256 mm, flip angle = 8 degrees | Cortical segmentation, & parcellation, & gray matter-white matter contrast |
| General Electric (San Diego) | T1-weighted IRSPGR | TR = 7.38 ms, TE = 2.984 ms, TI = 640 ms, 166 slices, voxel size = 0.94 × 0.94 × 1.2 mm, FOV = 240 mm, flip angle = 8 degrees | Cortical segmentation & parcellation, & gray matter-white matter contrast |
| Siemens (Minnesota & Atlanta) | T1-weighted MPRAGE | TR = 2170 ms, TE = 4.33 ms, TI = 1100 ms, 192 slices, voxel size = 1x1x1mm, FOV = 256 mm, flip angle = 7 degrees | Cortical segmentation & parcellation, & gray matter-white matter contrast |

(Schaer et al., 2008). LGI can range between 1 and 5. An LGI of 5 indicates that there is 5 times more cortex contained within the sulci than the amount of cortex on the outer surface (representing a deeply folded region); in contrast, an LGI of 1 represents a totally smooth region of cortex (Schaer et al., 2012). LGI is an improvement over two-dimensional cortical folding models such as the Gyrification Index (GI) (simply the ratio between the white matter/gray matter boundary and the pial boundary of the brain determined by 2-D coronal sections (Zilles et al., 1988)) because it takes into account the three-dimensional nature of the cortical surface (Schaer et al., 2008) and allows for regionally-specific measurements.

### 2.5. Statistical analysis

Analyses were carried out with the MATLAB Statistics Toolbox (MATLAB, 2015), IBM SPSS Version 22, and FreeSurfer version 5.3.0. Subject characteristics were analyzed using chi-square or independent samples *t*-tests as shown in Table 1.

Whole brain LGI comparisons across groups were performed with FreeSurfer. Because the LGI computation itself is relatively smooth (Schaer et al., 2012), no additional smoothing was applied. General linear model (GLM) analyses were conducted using FreeSurfer. Separate GLM analyses were used for right and left hemispheres. Group differences between the PAE and control groups were tested, statistically controlling for two factors: study site and sex. In addition, age and total intracranial volume (TIV) were entered as covariates to control for potential confounding. Prior to analysis, the two covariates (age and TIV) were normalized by subtracting each value by the mean and dividing by the standard deviation (creating z-scores). The analyses controlled for TIV because PAE is known to be associated with below-average head circumference and brain volumes (Roussotte et al., 2012). Group (PAE vs. control) was the independent variable. These analyses were performed using a manually created design matrix.

FreeSurfer offers two types of analyses, both based on General Linear Models (GLM): a Different Offset - Different Slope (DODS) model and Different Offset - Same Slope (DOSS) model. DODS includes more regressors and is thus a less powerful, more conservative approach than DOSS, which is a more liberal model that assumes similar slopes for the covariates. We chose to use a hybrid model in between DODS and DOSS to maximize power and to best adhere to the data. Each linear model incorporates two parameters: an offset (or intercept) and a slope. In this case, the offset/intercept was the LGI at a covariate of 0 (z-scored age) and is measured in the same units as LGI (mm). The slope reflects the relationship between the two factors (in this case LGI and age - measured in mm/year). The model was specified to allow for different offsets (i.e. y-intercept differences) amongst all factors; however the slope was constrained across study sites because there was no evidence of systematic differences in the relationship between age and LGI by site (nor would one assume there to be a difference). Results from each GLM were corrected for multiple comparisons with a two tailed Monte Carlo simulation implemented in FreeSurfer (Hagler et al., 2006) using a cluster-wise forming threshold of $p < 0.05$ and 10,000 random permutations. Results were visualized by overlaying significant clusters on top of an inflated cortical surface in the visualization tool Freeview.

Additionally, two separate Pearson product-moment correlations were performed to examine the relationship between LGI and IQ. First, for each cluster derived from the prior analysis of the group difference (PAE vs. control) in LGI, mean LGI was computed per participant. Pearson product-moment correlations were performed to assess the relationship between mean LGI and IQ. In a separate analysis designed to examine the spatial pattern of the relationship between IQ and LGI, a whole brain vertex-by-vertex analysis of LGI by IQ Pearson product-moment correlation was performed using the Query Design Estimate Contrast (QDEC) interface tool from FreeSurfer. GLMs were run separately for right and left hemispheres. IQ was normalized by transforming to a z-score and entered as a covariate. In these analyses, no other covariates (age or TIV) or factors (gender, study site, diagnosis) were included in the GLM. For multiple comparison control, a two-tailed false discovery rate (FDR) correction was implemented (Genovese et al., 2002) using a corrected *p*-value of $q = 0.05$. Results were visualized in QDEC.

## 3. Results

### 3.1. Subject characteristics

As shown in Table 1, the PAE and control groups did not differ in sex, race, ethnicity, handedness, socioeconomic status (SES), distribution across study sites, or total intracranial volume. It is worth noting that the lack of difference in SES (some studies find lower SES in alcohol-exposed individuals) was likely due to the high proportion of PAE group having been adopted by families with higher SES.

By chance, the control group was older than the PAE group by approximately one year; as a result, subsequent analyses controlled for age in addition to other potential confounds. In addition, a small significant difference in Puberty Development Scale score (Table 1) was found. A set of exploratory analyses were conducted to determine if puberty status explained a significant amount of variance in LGI - independently of age. Ultimately, a set of partial correlations revealed that age, but not puberty status, explained a significant amount of variance in LGI. As a result, age was included in the statistical models but puberty status was not included.

Although there was no overall group difference in racial makeup, there were significantly more controls that identified as Asian compared to those with PAE. As expected, participants in the PAE group had significantly lower IQ compared to controls (14 points, or nearly one standard deviation lower) as well as significantly higher incidence of microcephaly. A one-way ANOVA revealed a modest IQ difference across study sites [$F(3, 171) = 3.55$, $p < 0.05$] which reflects slight differences in the populations. The mean IQs were: Atlanta = 89.9; Los Angeles = 94.9; San Diego = 95.7; Minnesota = 100.9.

In addition to alcohol, prenatal exposure data for other toxins/substances were acquired. Exposure was reported as follows: amphetamines (1 control, 12 PAEs), cocaine (1 control, 21 PAEs), marijuana (1 control, 26 PAEs), tobacco (5 controls, 45 PAEs), caffeine (42 controls, 23 PAEs), hallucinogen (1 PAE), heroin (1 PAE), painkillers/opioids (2 PAEs), and tranquilizers (5 PAEs).

### 3.2. Motion and data quality

All FreeSurfer automated segmentation and parcellation results were visually inspected for accuracy/artifact. Seven participants were excluded from the analysis due to aberrant FreeSurfer processing, mostly due to the effects of excessive motion during scanning. The excluded participants were as follows: 5 PAE and 2 Controls; 6 males and 1 female; 1 from Atlanta; 0 from Los Angeles; 3 from Minnesota; and 3 from San Diego. No significant difference was found between the included and excluded participants in terms of sex [$\chi^2 = 2.98$, $p = 0.085$], race [$\chi^2 = 6.24$, $p = 0.397$], ethnicity [$\chi^2 = 1.58$, $p = 0.455$], history of prenatal alcohol exposure [$\chi^2 = 1.41$, $p = 0.704$], FASD Diagnosis [$\chi^2 = 4.44$, $p = 0.108$], age [$t(180) = 1.10$, $p = 0.273$], or IQ [$t(180) = 0.829$, $p = 0.408$].

### 3.3. Cortical gyrification in PAE vs. controls

Controlling for sex, site/scanner, age, and total TIV, the PAE group showed significantly lower LGI across large regions of cortex compared to the control group (cluster forming threshold was set to $p < 0.05$ and clusters were corrected for multiple comparisons with a Monte Carlo procedure as described earlier). Clusters are illustrated in Fig. 1. Five large clusters of significantly different LGI were evident (Table 3): three in the left hemisphere [all $p < 0.01$; sizes 26,684 and 3720, and

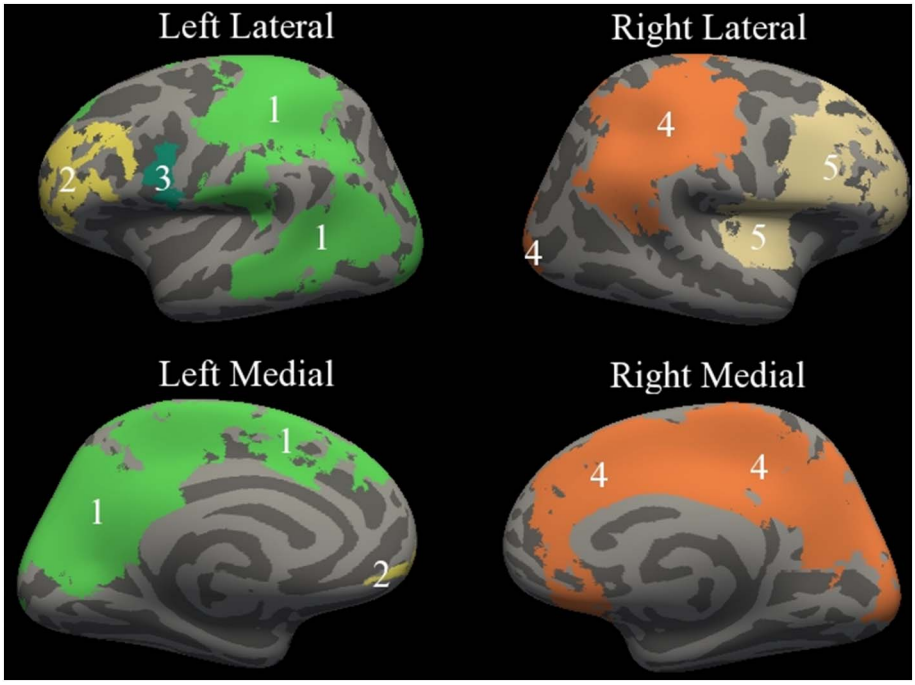


**Fig. 1.** Cortical gyrification group comparison between PAE and control groups.
Inflated cortical convolution maps showing clusters after thresholding the uncorrected data and correcting for multiple comparisons, (cluster form threshold, $p < 0.05$; clusters for multiple comparisons, $p < 0.05$) of significant reduction in gyrification amongst participants with prenatal alcohol relative to healthy controls. Cluster numbers correspond to those found in Table 3.

731mm$^2$], and two in the right hemisphere [$p < 0.001$; sizes 22,912, and 8780mm$^2$]. Cluster #1 had a peak vertex located within the left postcentral gyrus with the cluster covering portions of the left supramarginal, cuneus, precuneus, paracentral lobule, posterior cingulate, isthmus cingulate, and bank of the superior temporal, middle temporal, inferior temporal, inferior parietal, superior parietal, lateral occipital, and superior frontal gyri. Cluster #2 had a peak vertex within the left rostral middle frontal gyrus with the clusters comprising portions of the left frontal pole, pars opercularis, pars orbitalis, pars triangularis, and medial orbitofrontal gyrus. Cluster #3 was a very small cluster with a peak vertex within the left precentral gyrus. Cluster #4 had a peak vertex within the right postcentral gyrus, and encompassed portions of the cuneus, pericalcarine, paracentral lobule, posterior cingulate, caudal anterior cingulate, isthmus cingulate, rostral anterior cingulate, supramarginal, and medial orbital frontal, superior frontal, lateral occipital, superior parietal, inferior parietal, postcentral, and precentral gyri. Finally, Cluster #5 had a peak vertex located within the right rostral middle frontal gyrus, and included portions of the pars opercularis, pars triangularis, insula, and caudal middle frontal, superior frontal, and, superior temporal gyri.

### 3.4. Cluster-wise LGI by IQ correlational analysis

After extracting average LGI for each cluster from the group comparison, correlational analyses were performed. Pearson product-moment correlations were computed to assess the relationships between average LGI in each of the five clusters and IQ score (see Table 4A). In the left hemisphere, there was a positive correlation between LGI and IQ in cluster 1 (peak vertex within the left postcentral gyrus), [all participants: $r = 0.35$, $n = 175$, $p < 0.00001$; controls: $r = 0.29$, $n = 83$, $p < 0.01$; PAE: $r = 0.27$, $n = 92$, $p < 0.01$]; cluster 2 (peak vertex within the left rostral middle frontal gyrus), [all participants: $r = 0.38$, $n = 175$, $p < 0.00001$; controls: $r = 0.29$, $n = 83$, $p < 0.01$; PAE: $r = 0.33$, $n = 92$, $p < 0.01$]; and cluster 3 (peak vertex within the left precentral gyrus), [all participants: $r = 0.29$, $n = 175$, $p < 0.0001$; controls: $r = 0.17$, $n = 83$, $p = 0.12$; PAE: $r = 0.29$, $n = 92$, $p < 0.01$]. In the right hemisphere, there was also a positive correlation in cluster 4 (peak vertex within the right postcentral gyrus), [all participants: $r = 0.30$, $n = 175$, $p < 0.0001$; controls: $r = 0.23$, $n = 83$, $p < 0.05$; PAE: $r = 0.25$, $n = 92$, $p < 0.05$]; and cluster 5 (peak vertex within the right rostral middle frontal gyrus), [all participants: $r = 0.40$, $n = 175$,

**Table 3**
Cluster summary.
Clusters showing differences between the PAE and Control groups controlling for study site, sex, age, and total intracranial volume (TIV) (cluster forming threshold, $p < 0.05$; clusters for multiple comparisons, $p < 0.05$).

| Peak vertex cluster | Cluster number | Size (mm$^2$) | Number of vertices | Peak vertex MNI (x,y,z) | Clusterwise *p*-value | Findings |
|---|---|---|---|---|---|---|
| L postcentral | 1 | 26,684 | 55,883 | (−27.8, −35.1, 58.8) | 0.00020 | Con > PAE |
| L rostralmiddlefrontal | 2 | 3720 | 5499 | (−22.6, 49.3, 21.9) | 0.00020 | Con > PAE |
| L precentral | 3 | 731 | 1681 | (−46.7, 2.2, 22.5) | 0.00340 | Con > PAE |
| R postcentral | 4 | 22,912 | 49,464 | (37.3, −30.2, 64.0) | 0.00020 | Con > PAE |
| R rostralmiddlefrontal | 5 | 8780 | 17,431 | (35.2, 28.9, 40.6) | 0.00020 | Con > PAE |

Note: R = right hemisphere, L = left hemisphere; Con = Control group, PAE = Prenatal Alcohol Exposure group, MNI = Montreal Neurological Institute (coordinate system). Monte Carlo Z Simulation test was applied for multiple comparisons. Confidence interval was 90% for all clusters, and had the following ranges for each respective clusterwise *p*-value: 0.00020 (0–0.00040), and 0.00340 (0.00240–0.00440).

**Table 4**
Correlation summary.

A. Pearson product moment correlations following extraction of average LGI by participant within each significant cluster (Table 3 or Fig. 1) at the population ($n$ = 175), PAE ($n$ = 92) and Control ($n$ = 83) levels.

| Peak vertex cluster | Cluster number | $r$ - Pop. | $r$ - Controls | $r$ - PAEs |
|---|---|---|---|---|
| L postcentral | 1 | 0.35***** | 0.29** | 0.27** |
| L rostralmiddlefrontal | 2 | 0.38***** | 0.29** | 0.33** |
| L precentral | 3 | 0.29**** | 0.17 | 0.29** |
| R postcentral | 4 | 0.30**** | 0.23* | 0.25* |
| R rostralmiddlefrontal | 5 | 0.40***** | 0.43**** | 0.25* |

B. Clusters (FDR correction for multiple comparisons, $q < 0.05$) showing LGI by IQ correlations per vertex.

| Peak vertex cluster | Cluster number | Size ($mm^2$) | Number of vertices | Peak vertex talairach (x,y,z) |
|---|---|---|---|---|
| L banksts | 1 | 61,234.90 | 117,392 | (− 43.0, − 48.3, 12.4) |
| R parsopercularis | 2 | 54,388.46 | 105,027 | (36.1, 9.5, 11.5) |

Note: R = right hemisphere, L = left hemisphere; Con = Control group, PAE = Prenatal Alcohol Exposure group, Pop. = population. $p < 0.05$ = *, $p < 0.01$ = **, $p < 0.001$ = ***, $p < 0.0001$ = ****, $p < 0.00001$ = *****.

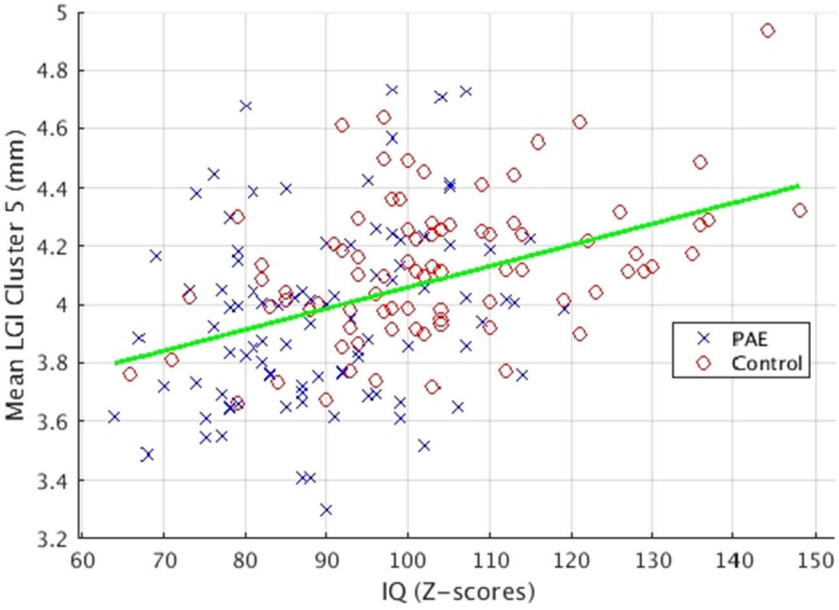


**Fig. 2.** Mean LGI Cluster 5 and IQ correlation.
Representative scatter plot of cluster 5 corresponding to that found in Table 3. Participants with PAE are indicated by a blue "x", and controls are indicated by a red "o". The solid green line represents the correlational fit to the entire dataset (i.e. both PAE and Control groups). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

$p < 0.00001$; controls: $r = 0.43$, $n = 83$, $p < 0.0001$; PAE: $r = 0.25$, $n = 92$, $p < 0.05$]. For illustration, a representative scatter plot of cluster 5 is included in Fig. 2 to provide a visualization of these data. Overall, there was a strong positive correlation between LGI and IQ score bilaterally. Lower LGI (smoother cortex) was associated with lower IQ scores.

### 3.5. Vertex-wise LGI by IQ correlational analysis

An alternative approach to examining/visualizing associations with surface data such as LGI is to examine it at the level of individual vertices (points) rather than whole clusters. QDEC was used to compute Pearson product-moment correlations between IQ and LGI at each vertex. For these analyses, only IQ was included as a covariate and no factors were controlled because the intention was to show an overall LGI by IQ correlation vertex by vertex. A false discovery rate was chosen to limit false positives to a corrected $p$-value of $q = 0.05$. Several cortical areas show a strong positive correlation between LGI and IQ – particularly the lateral aspects of the frontal, temporal, and parietal lobes bilaterally. Additionally, there were significant findings on the medial aspects bilaterally. Significant correlations were more widespread on the lateral aspects in both hemispheres. The findings on the medial aspects were more localized to the cuneus, precuneus, and the superior and inferior frontal regions. Findings are illustrated in Fig. 3A and B. Additional information regarding the findings can be found in Table 4B.

## 4. Discussion

This large-scale examination of cortical development and cognition in children with PAE adds to the understanding of the origins of cognitive deficits in FASD and suggests that further investigation of complex cortical morphometry is warranted. We applied three-dimensional surface MRI techniques to measure cortical gyrification in children and adolescents with PAE compared to controls. Controlling for age, brain volume, sex, and study site, the PAE group showed significantly smoother cortices bilaterally compared to controls. Collectively, the significant clusters spanned 48.7% of the right hemisphere, and 47.6% of the left hemisphere. These large effects were more pronounced and widespread than previous findings reported in the

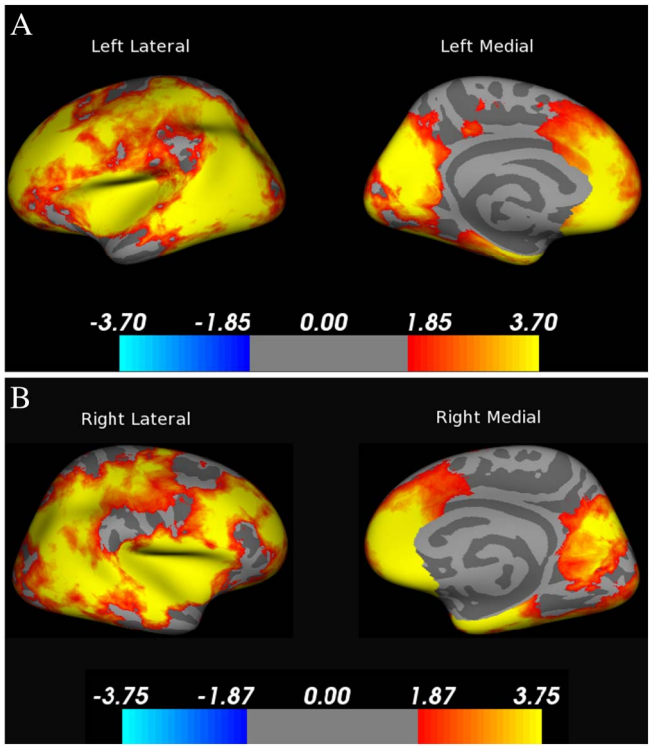


**Fig. 3.** Vertex-wise IQ by LGI correlations.
(A-B): Inflated vertex-wise cortical convolution maps showing correlations between IQ and LGI amongst all participants in the left (A) and right hemisphere (B). An FDR of $q < 0.05$ was employed to correct for multiple comparisons. Color codes are in negative logarithms ("-log") and represent strength of significance with warm colors for positive associations and cool colors for negative associations. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

literature (Infante et al., 2015; Rajaprakash et al., 2014). A likely explanation for the size of the effects in the current data is the relatively large sample size which resulted in greater statistical power to detect effects in a set of vertex-wise analyses.

Although the specific mechanisms responsible for cortical malformations in PAE are not yet known, it is worth noting that there is a known association with microcephaly (which also occurs in PAE). Previous studies have shown that individuals with microcephaly have significantly smoother cortices than those with average brain volumes (Germanaud et al., 2014; Germanaud et al., 2012; Toro et al., 2008) suggesting that early insults may sometimes contribute to both brain anomalies. In the current study, we did not observe significantly lower brain volume in PAE compared to controls, perhaps because we had a relatively small number of full FAS diagnoses in the sample. Nonetheless, the LGI analyses were all controlled for total intracranial volume, increasing confidence in the results showing that those with PAE have cortical smoothing that is more extreme than is accounted for by their brain sizes.

The complex cortical folding that was measured here and in other studies of children and adolescents is the result of processes that begin very early in gestation but continue into the second and third trimester in humans. Cell proliferation in the germinal ventricular zone occurs as early as week 4 (Bystron et al., 2008) and continues into the second trimester for 8 to 16 weeks. Cells gradually migrate to the sub-plate, which will eventually become the cerebral cortex (Marsh et al., 2008). Next, migration and synaptogenesis occur, with neurons extending axons and forming synapses. Connections within the cortex as well as between cortex and sub-cortical regions, brainstem, cerebellum, and spinal cord are established (Fogliarini et al., 2005). The majority of cortical folding (the actual formation of sulci and gyri) occurs between gestational week 20 and 35 (Garel et al., 2003), and the brain transitions from lissencephalic ('smooth brain') to convoluted. Lastly, myelination occurs (Kinney et al., 1988; Kinney et al., 2001). Ultimately, the purpose of cortical folding is to maximize cortical surface area and ensure maximum information processing efficiency. Gestational timing is not only an important aspect of cortical gyrification development, but it is also especially relevant to understanding developmental insults like PAE.

Critical periods, during which there is increased vulnerability to insult, have been identified for a range of developmental processes during gestation. PAE in mice on the 7th day of gestation produces brain alterations akin to those seen in children with FASD as well as facial dysmorphia (Sulik and Johnston, 1983). On the 7th day of mouse gestation, cellular proliferation and migration are occurring in the forebrain, midbrain, and hindbrain (Rice and Barone, 2000). In a first-trimester equivalent study, alcohol exposure between gestational days 20 and 32 in pigtail macaques also produces an FAS-like syndrome (Clarren et al., 1988). As the literature has generally shown (Coles, 1994), first trimester human alcohol exposure impacts a number of important developmental processes that can profoundly disrupt later development.

The first trimester is clearly one critical period for human cortical development because cellular proliferation and migration are occurring. Disruptions in cellular proliferation lead directly to abnormalities in migration (Rice and Barone, 2000). Early rodent models indeed demonstrated significant abnormalities in neuronal migration resulting from PAE (Miller, 1993). In its extreme form, disrupted neuronal migration is associated with severe cortical abnormalities including lissencephaly, or 'smooth brain' (Tau and Peterson, 2010) – a condition in which the absence of cortical gyrification results in severe intellectual impairment or even non-viability of the individual (Olson and Walsh, 2002). As indicated previously, however, cortical development can also be disrupted in the second and third trimesters via alcohol's effects on neuronal migration and other processes involved in folding.

Beyond the most extreme case of absent cortical gyrification, there is evidence of associations between a wide range of cortical abnormalities and cognition. For example, previous research has shown that cortical folding affects later functional development (Dubois et al., 2008) in a manner that affects intelligence. Polymicrogyria (an abnormality in neuronal migration that results in an increase in the number of gyri) has been observed in a 16 year old female with PAE who met full FAS diagnostic criteria (Reinhardt et al., 2010). Reinhardt and colleagues suggested that FAS should, in fact, be considered as part of the differential diagnosis process in cases where polymicrogyria has been identified. Cortical abnormalities such as polymicrogyria are associated with general neurologic disruption including seizures, hypotonia, and problems with speech and swallowing (Chang et al., 2004). An animal model of FAS showed polymicrogyria in the frontal lobe, pachygyria (reduced number of gyri) in the parietal lobe, and agyria (absence of gyri) in the occipital lobe of infant pigtail macaques exposed prenatally to alcohol (Clarren and Bowden, 1984). Of course, abnormal cortical gyrification is not specific to FASD and has been shown to occur in several clinical populations including schizophrenia (Palaniyappan and Liddle, 2012), 22q11.2 deletion syndrome (Schaer et al., 2009), autism spectrum disorder (Jou et al., 2010), Williams syndrome (Thompson et al., 2005), and mental retardation (Zhang et al., 2010) amongst others.

In addition to finding significantly reduced cortical gyrification in children with PAE, we demonstrated a clear relationship between cortical gyrification development and global cognitive functioning (IQ). The association was in the anticipated direction, such that smoother cortex (reflecting developmental abnormality) was strongly associated with lower IQ. Alcohol-related disruptions to critical early neurodevelopmental processes including cell proliferation, neuronal migration, and cortical folding would be expected to have a generalized, long-term impact on the individual's functioning because they are "foundational" disturbances. Overall, we did not observe a regional

pattern to the cortical abnormalities nor did we find that global cognitive functioning was associated with gyrification in a regional pattern. Clearly, the literature suggests that PAE is associated with a wide range of possible insults to brain development and it is likely that the clinical variation seen in FASD is a result of varying combinations of insults and timing of insults during early development. Cortical gyrification is but one of those insults and, as such, represents a relatively blunt indicator of neurodevelopmental insult.

As mentioned previously, cortical folding/gyrification is an evolutionary adaptation to maximize the amount of cortex within the available space of the cranium (Mota and Herculano-Houzel, 2012; Welker, 1990) and is thought to directly contribute to increased efficiency of information processing by optimizing the length and the layout of intra-cortical connections (Goldman-Rakic, 1981; Rademacher et al., 1993; Rakic, 1988; Richman, Stewart, Hutchinson, & Caviness, 1975; Roland and Zilles, 1994; Van Essen, 1997; Watson et al., 1993); for a review, see (Zilles et al., 2013). Cortical gyrification is inherently linked to cognitive functioning, as suggested by non-human primate studies (Rilling and Insel, 1999; Zilles et al., 1989) as well as human studies (Luders et al., 2008). It is worth noting that Luders and colleagues found more modest associations between cortical gyrification and intelligence and the effects were more localized than we observed in PAE. This difference may be due simply to the wider range of gyrification and wider range of IQ in our sample (which contained both typically-developing children and those with PAE).

One limitation of the current study, faced by many studies of FASD, is the relative lack of detail about alcohol exposure in most cases. This prevented us from conducting analyses examining the relationship between exposure amounts/timing and cortical development. In this type of neuroimaging study, an added limitation arises from lost data for some participants. In some cases, detailed cortical measurements were not obtained because of processing difficulties – most often because of motion artifact (which occurs in both PAE and control groups). We did evaluate motion as a potential confound, and we determined that there were not significant differences in motion between the PAE and control groups. Nonetheless, the lost data do temper the generalizability of the study slightly.

By chance, our groups ended up with a significant age difference – with the PAE group being younger than the controls by about one year. We evaluated the impact of age as well as puberty on our outcome measures and, ultimately, included age as a factor in all of our statistical models. Although statistical control is not a perfect substitute for precisely matched groups, our analyses suggests that these statistical controls allow us to interpret our results with confidence in this case. Another potential limitation of a multi-site study such as this one relates to systematic measurement differences across sites. We did observe a difference in LGI across sites, which could be due to hardware differences, minor differences in acquisition sequences, or population differences across the sites. We took a conservative approach and controlled for site in all of our statistical models. Overall, the data seem to suggest that semi-automated cortical characterization of this type is relatively robust in a clinical population such as FASD across multiple scanner sites. A further methodological consideration pertaining to the current study is the lack of a definitive significance threshold for analyses such as the vertex-wise analyses presented here. Our approach was a conservative one in which we applied a commonly-used false discovery rate correction in one case and a commonly-used Monte Carlo simulation technique in another. Because of the size of the effects seen here and the conservative nature of the corrections, we have confidence in the conclusions. Lastly, although our study included a relatively large sample size, breaking down the FASD group into subgroups (i.e. FAS, non-FAS, and deferred) was not possible because of the resulting small group sizes. Therefore, we were unable to determine if there is a relationship between FASD severity and cortical gyrification. CIFASD plans to continue to acquire new participants with FASD who will undergo neuroimaging, so it will be possible to address these questions in the future.

## 5. Conclusion

The current study examined cortical gyrification in PAE, and explored relationships with cognitive functioning. The data showed robust effects of smoother cortices in PAE compared to controls. These data add to the existing literature showing cortical gyrification abnormalities in PAE and provide a clear example of how alcohol interferes with basic neurodevelopmental processes that ultimately have large downstream effects. One of these effects is illustrated in the strong associations seen between cortical gyrification and IQ. Ultimately, measures of cortical gyrification may be useful as indices of the overall level of neurodevelopmental abnormality in individuals with FASD.

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### *Conflict of interest*

None of the authors has a relevant conflict of interest to disclose.

### *Ethical approval*

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

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