

# Longitudinal Structural Brain Changes in Children and Adolescents with Prenatal Alcohol Exposure

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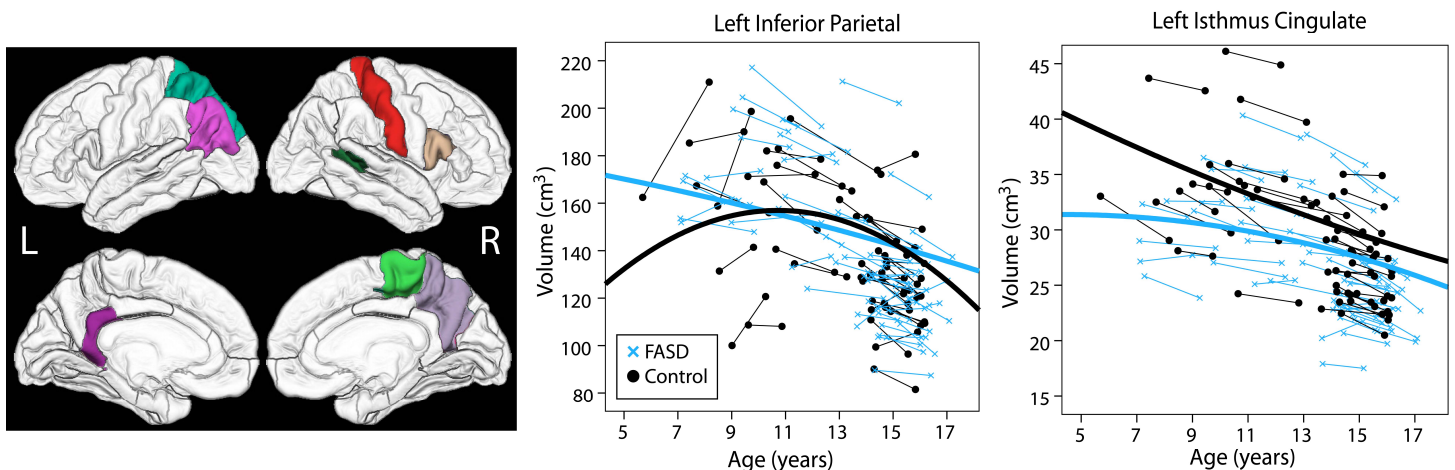
**INTRODUCTION:** Children and adolescents with prenatal exposure to alcohol often exhibit cognitive, behavioral and neurological problems relative to controls<sup>1</sup>, including structural brain differences such as reduced brain volume<sup>2-4</sup> and abnormal cortical thickness<sup>5,6</sup>. Although studies report abnormalities over a range of ages, the trajectory of brain development in subjects with fetal alcohol spectrum disorders (FASD) remains unclear. In healthy subjects, the cortex thickens then thins with age, following nonlinear trajectories that vary regionally<sup>7</sup>. A recent cross-sectional study including subjects overlapping with those of the current investigation demonstrated thicker cortices in FASD in bilateral inferior frontal regions, but effects of age were not examined<sup>8</sup>. Another cross-sectional study found age-related cortical thinning in subjects with FASD, though trajectories did not differ significantly from controls<sup>5</sup>. Longitudinal investigations provide increased statistical power for detecting more subtle differences in brain structure across time, and thus our goal was to investigate trajectories of cortical volume changes in subjects with prenatal alcohol exposure compared to unexposed controls.

**METHODS:** This study included 87 subjects from three sites. Subjects were initially aged 5.7-16.3 years ( $12.4 \pm 2.6$ ) and were each scanned twice (mean gap=1.8 yrs) at the same site. T1-weighted MRI data was collected in Los Angeles (n=32, 17m/15f, 23 FASD/9 control), San Diego (n=6, 4m/2f, 2 FASD/4 control), and Cape Town (n=49, 25m/24f; 24 FASD/25 control) on 1.5T Siemens Sonata, 3T GE Signa and 3T Siemens Allegra MRI scanners, respectively. Parameters for LA/SD/CT were TR=1900/7.8/2200 ms, TE=4.38/3.0/5.16 ms, flip angle 15°/12°/12°, voxel size 1x1x1/0.94x0.94x1/1x1x1 mm, acquisition time 8:08/7:24/7:04. Data was processed in the FreeSurfer v5.1 longitudinal processing stream to extract 66 cortical volumes (33 per hemisphere). A preliminary mixed models analysis tested each region for age-related volume changes in either group, controlling for site, at  $p < 0.00076$  ( $p < 0.05$  corrected for 66 comparisons). Only regions with significant age effects were analyzed for age-by-group or age<sup>2</sup>-by-group interactions; this threshold was set to  $p < 0.05$ , given previous correction at the age effects stage and the exploratory nature of these comparisons.

**RESULTS/DISCUSSION:** Of 66 total regions, 37 had significant age-related changes in the exposed and/or control groups. Of these, eight demonstrated significant interaction terms (Fig. 1). The left inferior and superior parietal, right bank of the superior temporal sulcus, right pars opercularis, right paracentral, right postcentral, and right precuneus regions had significant age<sup>2</sup>-by-group interactions in which control subjects had quadratic trajectories with increases then decreases, while FASD subjects demonstrated more steadily declining volumes (e.g., inferior parietal region, Fig. 1). In the left isthmus cingulate, age-by-group and age<sup>2</sup>-by-group interactions were significant; both groups had volume declines across the age range, though they were steeper in controls (Fig. 1).

Most changes were observed in parietal lobes, areas known to be abnormal in FASD<sup>3,6</sup>. The smaller overall volume changes in FASD subjects suggest reduced cortical plasticity, and may help reconcile discrepancies in previous findings which report both increased<sup>6,8</sup> and decreased<sup>5</sup> cortical thickness in FASD relative to controls. Although not significantly different here ( $IQ_{FASD} = 77 \pm 20$ ;  $IQ_{control} = 80 \pm 24$ ;  $p = 0.5$ ), subjects with FASD generally have lower IQ than controls, which may contribute to the observed trajectory differences, given similar observations in healthy subjects with superior intelligence versus those with average intelligence<sup>9</sup>.

**CONCLUSIONS:** In the first longitudinal study of cortical development in prenatal alcohol exposure, we demonstrate several regions with different developmental trajectories from controls, implying reduced brain plasticity in subjects with prenatal alcohol exposure. This suggests that early treatments and interventions may have more impact, and ultimately be more beneficial in this population.



**FIGURE 1:** Age by group and/or age<sup>2</sup> by group interactions were significant in eight regions: the left superior parietal (teal), left inferior parietal (pink), left isthmus cingulate (purple), right posterior bank of the superior temporal sulcus (dark green), right postcentral (red), right pars opercularis (beige), right paracentral (light green) and right precuneus (gray). These areas had different trajectories for FASD and control subjects, as shown in two example areas.

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