Diffusion Tensor Imaging Correlates of Mathematical Ability in Children with Fetal Alcohol Spectrum Disorder

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INTRODUCTION: Fetal alcohol spectrum disorder (FASD) is the umbrella term describing the various developmental disorders associated with prenatal alcohol exposure. Children with FASD are delayed in many cognitive domains[1], but the effects of prenatal alcohol exposure on mathematical development seem to be particularly strong[2]. Mathematical ability has been linked to prefrontal and parietal brain regions, in particular the intraparietal sulcus, in both functional[3] and structural[4] imaging studies. Diffusion tensor imaging (DTI), a sensitive measure of white matter microstructure, has demonstrated that mathematical ability is correlated with white matter structure in the left parietal lobe of children with Velocariofacial syndrome (aged 7-19 years)[5], and in the left corona radiata and inferior longitudinal fasciculus in healthy children (aged 7-9 years)[6]. There has been speculation that abnormal parietal brain function may be related to mathematical difficulties in FASD[7]; however, math deficits in children with FASD have yet to be linked to underlying brain structure. The purpose of this study was to correlate white matter DTI parameters with mathematical ability in children with FASD.

METHODS: Subjects were 21 children aged 5-13 years (12m/9f) diagnosed with FASD. Subjects underwent cognitive tests including the Woodcock-Johnson III Quantitative Concepts test of mathematical ability. Scores were compared to the normal mean score (100) with a one-sample t-test. DTI was performed on a 1.5T Siemens Sonata scanner using dual spin echo EPI, 40 3mm slices (no gap), image matrix 96x128 zero-filled to 256x256, TE/TR=98ms/6400ms, b=1000 s/mm^2, 8 averages and 6 directions, 6:06 min acquisition. Non-diffusion weighted images (b=0 s/mm^2) were normalized to the ICBM EPI template with non-affine transformations in SPM5; fractional anisotropy (FA) maps were normalized with the same parameters, and smoothed with a 4 mm kernel. Voxel-based correlation of FA with normalized math scores, controlling for age, was performed in SPM5. Only voxels considered to be white matter (FA$\geq$0.2) in all individuals were included. An F-test with $p<0.05$ per voxel and cluster size>59 (which Monte Carlo simulations showed gave an overall α=0.048) was used to determine significant clusters. Clusters were used as seeding regions for tractography.

RESULTS/DISCUSSION: Children with FASD scored significantly below average on the math test (mean±SD=87.1±16.5, p=0.002). Significant correlations of FA with arithmetic scores, controlling for age, were seen in both positive and negative directions in children with FASD. Three positive clusters and one negative cluster were observed (see Fig.1A,B): two positive clusters in the left parietal region (upper cluster of 114 voxels, lower cluster of 83 voxels), one positive cluster in the left cerebellum (186 voxels), and one negative cluster in the brain stem (110 voxels). Fiber tracking revealed that these clusters were part of the upper left corticospinal tracts/corpus callosum, left superior longitudinal fasciculus (SLF), middle cerebellar peduncles, and lower projection fibers, respectively (see Fig. 1C,D)

DTI has demonstrated correlations between regional brain FA and math scores in children with FASD for the first time. The two parietal clusters, the upper one very close to the intraparietal sulcus and the lower one within the fronto-parietal-temporal connection SLF, support previous findings in healthy children[6] and those with Velocardiofacial syndrome[5] and confirm earlier hypotheses about FASD[7]. A positively correlated cluster in the cerebellum was observed, suggesting this area is also related to math ability in FASD. The negatively correlated cluster in the lower projection may seem counterintuitive; however, other studies have also shown negative correlations between cognitive abilities and FA in a variety of areas[8, 9]. This study demonstrates that several different regions are related to math skills in children with FASD, supporting previous findings and highlighting further areas. These results will help to further understand the relationship between cognitive ability and underlying brain structure in children with FASD.

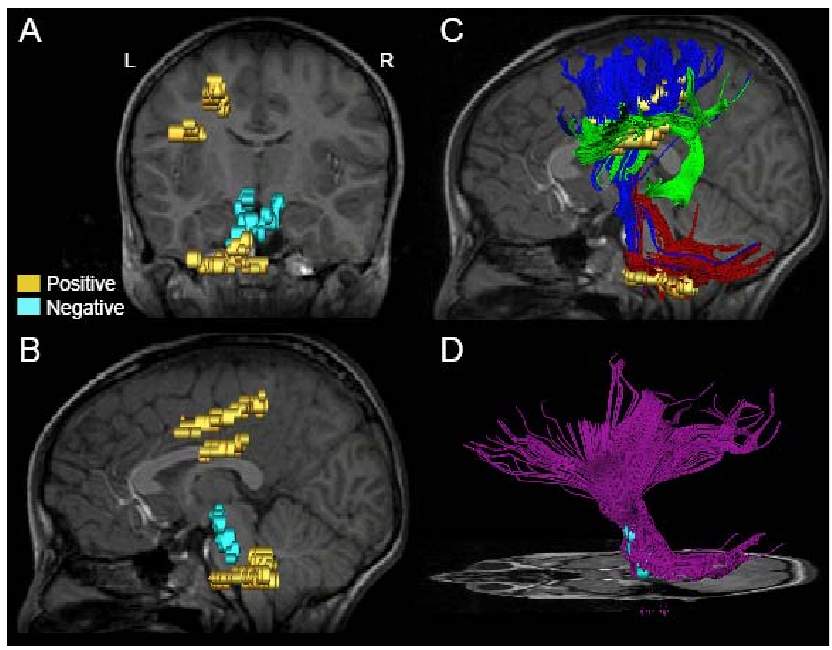

Figure 1: Clusters with significant correlations between fractional anisotropy and math ability are shown, for both positive (gold) and negative (cyan) correlations (A,B), along with all tracts produced when clusters were used as seeding regions for tractography (C,D). Three positive clusters were observed, containing the upper left corticospinal tracts/corpus callosum (blue), left superior longitudinal fasciculus (green), and middle cerebellar peduncle (red) fibers. One negative cluster was observed containing the lower projection fibres (purple).

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