Diffusion Tensor Tractography of Children with Fetal Alcohol Spectrum Disorder

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INTRODUCTION: Fetal alcohol spectrum disorder (FASD) is the umbrella term used to describe the various developmental disorders associated with prenatal alcohol exposure[1], and that often involve a variety of cognitive and behavioral deficits[2]. White matter tracts provide the brain connections necessary for proper cognitive function, and abnormalities such as reduced overall white matter volume, particularly in the parietal lobe[3], and agenesis or deformations of the corpus callosum[4,5] have been demonstrated in FASD. Diffusion tensor imaging (DTI) may provide a more sensitive measure of white matter microstructure than other techniques, and two previous DTI studies using 2D region-of-interest analysis have observed corpus callosum abnormalities in FASD[6,7]. However, neither study looked beyond the corpus callosum. Given the range of cognitive deficits associated with FASD, other white matter tracts are likely to be affected and warrant investigation. The purpose of this study was to determine the range of white matter tract abnormalities in children with FASD using DTI tractography.

METHODS: Subjects were 24 children aged 5-13 years (13m/11f) previously diagnosed with FASD and 95 healthy controls 5-13 years (50m/45f) with no history of neurological disease or injury. 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=1000s/mm^2, 8 averages and 6 directions, 6:06 min acquisition. Images were normalized to a homemade template using non-affine registration. Tractography was performed using a semi-automated method in which seeding, inclusion, and exclusion regions were drawn on the template FA map and automatically mapped to native space for each individual. Average values of fractional anisotropy (FA) and mean diffusivity (MD) were calculated in each individual for each of ten major white matter tracts: the cingulum, corticospinal tract (CST), superior and inferior longitudinal fasciculi (SLF, ILF), superior and inferior fronto-occipital fasciculi (SFO, IFO), uncinate fasciculus, and genu, splenium, and body of the corpus callosum (CC). Where appropriate, left and right sides were measured separately and, if paired t-tests were not significant, combined for further analysis. A full battery of cognitive tests was performed on each child with FASD, including measures of working memory, executive functioning, quantitative concepts and vocabulary. FA and MD were compared between groups with a multiple analysis of covariance (MANCOVA) controlling for age ($p<0.05$). White matter, gray matter, and total brain volume were measured using tissue segmentation of T1-weighted images, and compared between groups using a MANCOVA.

RESULTS/DISCUSSION: Significant reductions of FA were observed in the ILF, SLF, splenium of the CC, and right cingulum in children with FASD. MD was elevated in the IFO and the left ILF, whereas MD was reduced in the genu of the CC in children with FASD. In general, there was good agreement between left and right hemispheres for normal and abnormal diffusion parameters. FA reductions in FASD were on the order of 4-5%, while MD changes ranged from a 2% reduction to a 3% elevation. As expected, white matter, gray matter, and total brain volume were significantly reduced in the FASD group, by 11%, 7%, and 8%, respectively.

These results support previous DTI findings of callosal abnormalities in FASD[6,7] and, importantly, demonstrate diffusion changes beyond the corpus callosum for the first time. Although the percent changes of FA and MD are smaller than in previous studies[6,7], we averaged values over larger brain regions and more subjects, and included younger and less severely affected children than previous studies, and we demonstrate more widespread abnormalities across a broader range of subjects. Consistent with previous studies showing vulnerability of the temporal and parietal lobes[3,8], differences were observed in white matter connecting to the temporal region, specifically the cingulum, SLF, and ILF. An investigation of the eigenvalues in tracts that showed significant FA reductions revealed a consistent elevation of perpendicular diffusivity, suggesting fewer barriers to diffusion and perhaps decreased myelination in children with FASD. In conclusion, DTI has demonstrated abnormalities beyond those seen in conventional MRI studies[9], and may help to further understand the structural changes underlying the cognitive deficits associated with FASD.

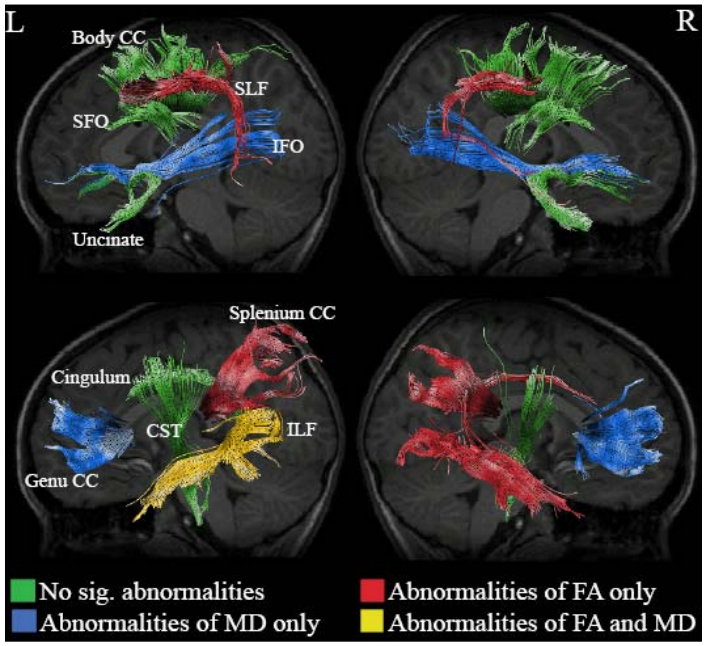

Figure 1: Several tracts had diffusion abnormalities in children with FASD. In general, there was good agreement between left and right hemispheres for both normal (SFO, CST, uncinate) and abnormal regions (SLF, IFO, ILF), although the cingulum had FA abnormalities on only the right side and the ILF had MD differences only on the left. The genu and splenium of the CC also demonstrated diffusion abnormalities. Tracts of an 8 year old male control are shown.

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