White Matter Alterations in Callosal Agenesis: A Diffusion Tensor Imaging Study

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Introduction

Agenesis of the Corpus Callosum (AgCC) is a congenital condition affecting roughly 1 in 4000 individuals. It is characterized by a partial or complete absence of the corpus callosum and is accompanied by a spectrum of neuropsychological deficits. While the absence of callosal fibers is clearly the most obvious anatomic feature, the wide range of clinical presentations of the condition suggests the involvement of other developmental abnormalities. The absence of the corpus callosum may be but one manifestation of a more widespread white matter developmental disorder. In this study we use diffusion tensor imaging (DTI) to analyze the microstructural white matter organization of subjects with AgCC. We perform 3D DTI fiber tracking of four white matter tracts, the Cingulum Bundle (CB), Inferior Fronto-Occipital Fasciculus (IFO), Uncinate Fasciculus (UF) and Arcuate Fasciculus (AF). From 3D tract-based measurements, we compare the fractional anisotropy (FA) of each tract in AgCC subjects with those of matched healthy controls.

Methods

DTI was performed on 12 healthy volunteers and 12 AgCC subjects, 8 with complete callosal agenesis and 4 with partial callosal agenesis. Subjects and controls were matched for age, gender and handedness. Exclusion criteria included full-scale IQ (WAIS III test) < 70. Whole-brain DTI was performed at 3 T with single-shot echo planar imaging, interleaved 1.8-mm axial sections with no gap, in-plane resolution of 1.8 x 1.8 mm with a FOV of 230 mm, and 55 diffusion-encoding directions at b = 1000 s/mm^2. An additional image was acquired without diffusion weighting (b = 0 s/mm^2). Scan data were analyzed using DTI Studio (http://www.mristudio.org), and color-coded FA maps were created. Tractography was performed with Fiber Assignment by Continuous Tracking, using the brute-force method in which tracks were seeded from all voxels in the brain with an FA value larger than 0.3. Fibers were tracked while voxel FA values exceeded 0.2 and turning angles between the primary eigenvectors of neighboring voxels were less than 50^0. Similar tracking parameters have been used in several recent studies[1,2]. Individual tracts were then selected by requiring fibers to pass through manually placed Region of Interests (ROIs) on DTI color maps, according to protocols specific for each tract (Fig 1). The FA for each tract was calculated from the 3D fiber tracking results as a weighted average, with the FA of each voxel weighted by the number of fibers passing through it. Group comparisons were then made using a Student's t-test (two-tailed), with group differences considered significant at p<0.05.

Results

In AgCC subjects, significant reductions in tract FA were found in both left and right CB, left IFO, and in the FA of both tracts averaged across hemispheres. Less pronounced FA reductions were observed in right AF and UF, although the AF result was only significant when all AgCC subjects were considered while the UF result was significant only when the comparison was confined to complete agenesis (Table 1).

Table 1: Average tract FAs. P-values from group comparisons are shown, with asterisks denoting significant results (*P<0.05; **P<0.01).

	Tract FA			***Group Comparisons***	
Tract	*Controls*	*All AgCC*	*Complete AgCC*	*Control vs. All*	*Control vs. Complete*
CB					
Right	0.553 ± 0.016	0.528 ± 0.033	0.530 ± 0.026	0.032 *	0.048*
Left	0.604 ± 0.024	0.570 ± 0.036	0.570 ± 0.014	0.015 *	<0.001**
Ave.	0.579 ± 0.014	0.548 ± 0.033	0.549 ± 0.018	0.015 *	0.0035**
IFO					
Right	0.550 ± 0.015	0.535 ± 0.023	0.540 ± 0.022	0.068	0.288
Left	0.570 ± 0.022	0.539 ± 0.022	0.544 ± 0.016	0.0027**	0.0081**
Ave.	0.560 ± 0.017	0.537 ± 0.019	0.542 ± 0.013	0.0050**	0.018 *
AF					
Right	0.505 ± 0.026	0.481 ± 0.030	0.480 ± 0.031	0.045 *	0.089
Left	0.544 ± 0.020	0.530 ± 0.036	0.534 ± 0.033	0.269	0.481
Ave.	0.524 ± 0.019	0.506 ± 0.029	0.507 ± 0.028	0.078	0.154
UF					
Right	0.483 ± 0.033	0.461 ± 0.016	0.459 ± 0.017	0.052	0.049 *
Left	0.506 ± 0.020	0.492 ± 0.034	0.488 ± 0.025	0.272	0.146
Ave.	0.495 ± 0.025	0.479 ± 0.023	0.474 ± 0.019	0.153	0.075

Discussion

Past DTI studies of schizophrenia have shown significant white matter alterations in specific tracts[3]. Our findings in both CB and IFO are identical to alterations in schizophrenics, each found in multiple studies. This result complements the genetic linkage between AgCC and schizophrenia[4]. Additionally, in CB and IFO, the left>right FA asymmetry normally seen in healthy controls was reduced in AgCC. This asymmetry is thought to play a role in hemispheric functional lateralization[2], and is lost in schizophrenia, so its reduction in AgCC could have significant cognitive effects that mimic those of schizophrenia.

Conclusions

Agenesis of the Corpus Callosum is correlated with microstructural alterations in white matter organization in addition to the absence of callosal fibers. Furthermore, the changes are tract-specific, and do not represent a uniform global disruption of white matter organization. Patterns of reduced FA are similar to those found in schizophrenia.

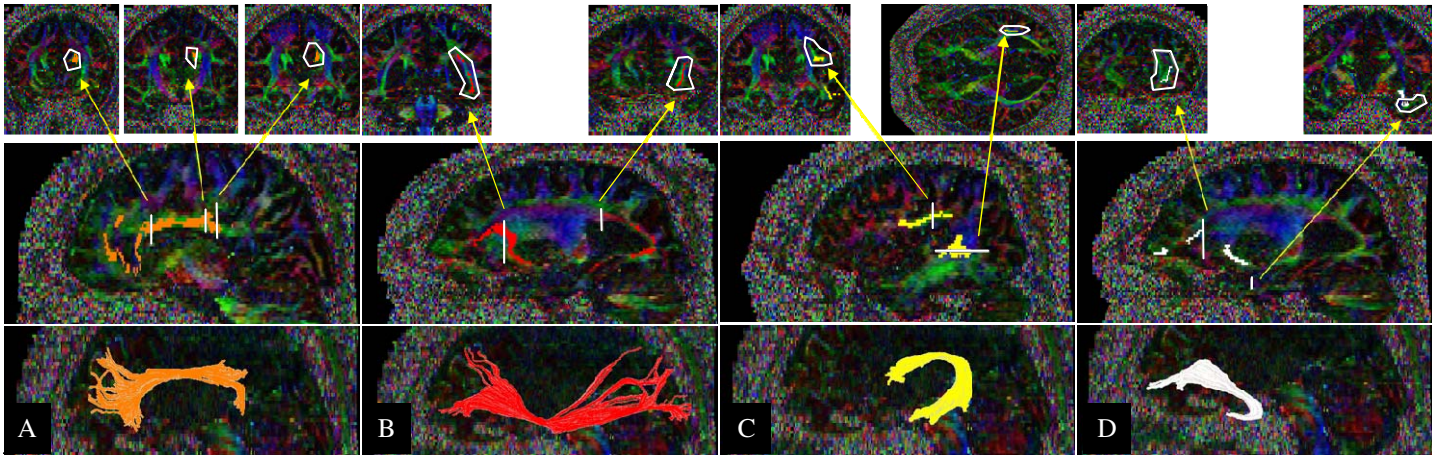

Figure 1. 3D Tract Reconstruction for CB (A), IFO (B), AF (C) and UF (D). ROIs manually drawn on coronal and/or axial slices (top row) are shown in relation to each other on a sagittal slice (middle row). Reconstructed 3D tract is overlaid on a sagittal slice (bottom row). Subject shown has AgCC.

References and Acknowledgements: [1] Wakana S et al. NeuroImage 2007;36:630-644. [2] Rodrigo S et al. AJNR 2007;28:1526-31. [3] Kubicki M et al. J Psych Res 2007;41:15-30. [4] Clapcote S et al. Genetics 2006;173:2407-10. This study was supported by grants from the NIH to EHS, the UCSF Strategic Opportunities Support Center of the Clinical and Translational Sciences Institute, and a grant from the American Society of Pediatric Neuroradiology.