FRACTIONAL ANISOTROPY REDUCTIONS OF DEEP WHITE MATTER IN VELOCARDIOFACIAL SYNDROME

Background

Velocardiofacial syndrome (VCFS, DiGeorge syndrome, 22q11 deletion syndrome) is associated with a deletion on chromosome 22. This deletion includes approximately 30 genes, and though symptoms vary widely in type and severity, individuals with VCFS do share some characteristic abnormalities in the heart, palate, and face, and generally have mild cognitive impairments. VCFS patients are also at much higher risk for psychosis, with a prevalence of 30% for schizophrenia-like psychosis (compared to 1% in the general population) (Walter et al., 2009).

Diffusion-weighted imaging (DWI) of the brain uses MRI to detect differences in fractional anisotropy (FA), which can indicate abnormalities in white matter. White matter abnormalities such as reduced FA have been implicated as part of the neurophysiology of psychosis.

Methods

Subjects  Nine non-psychotic VCFS subjects with confirmed chromosomal 22q11 deletion and nine healthy control (HC) subjects, matched for age, sex, and PSES.

DWI Acquisition  1.5T GE, resolution of 0.9375mm x 0.9375mm x 5mm.

Areas of Interest  White matter tracts of interest were determined from the results of tract-based spatial statistics (TBSS) (described in Kikinis et al., poster #74). TBSS was used to highlight areas of FA difference between groups (Fig. 1a), the results of which were co-registered to an atlas of average FA patterns across our caselast, and to a universal white matter atlas (i.e., the Montreal Neurological Institute atlas) (Fig. 1b). The atlas was then used to identify which tracts were likely driving the FA differences between groups. In the left parietal lobe, the cingulum, superior longitudinal fasciculus (SLF; not including the arcuate portion), inferior longitudinal fasciculus (ILF), and inferior fronto-occipital fasciculus (IFOF) were implicated. In the cerebellum, in both hemispheres, the short intracerebellar fibers were identified based on Kanaan et al., 2009.

Tractography  In 3D Slicer, streamlined tractography was performed on each fiber bundle of interest using manually traced regions of interest (ROIs) and exclusion regions (Fig. 2). Most ROIs were seeded 10 times, each time seeding from a new random start point within the selected voxels. Exceptions were the SLF and cerebellum, which were isotropically seeded once, due to the large number of tracts produced from one seeding session. Tracts of interest were isolated by selecting for tracts that passed through all ROIs and did not pass through exclusion regions. Fiber bundles often required minor manual edits. The cingulum could not be tracked in full, so it was tracked in dorsal and ventral portions.

Results

FA was significantly reduced in VCFS in the IFOF (p = 0.002) and the ventral cingulum (p = 0.028), and was reduced at a trend level in the ILF (p = 0.064) and right intracerebellar fibers (p = 0.102).

Discussion

Major Findings  Reduced fractional anisotropy in the IFOF and ventral cingulum in VCFS suggests the presence of abnormalities in the microstructure and/or organization of these fiber bundles. This may be part of the underlying pathophysiology involved in some of the cognitive impairments in VCFS, or may play a role in susceptibility to psychosis. Previous studies in schizophrenia have, for example, suggested that reduced FA, partly in the IFOF, correlates with executive function impairment in patients (Pérez-Iglesias et al., 2010).

Limitations and Future Directions  To confirm that differences are present only in the left longitudinal tracts, as suggested by the TBSS results, manual tractography should be performed in the right hemisphere, as well. Follow-up with these subjects may determine whether these abnormalities are involved in psychosis onset. Since neuropsychological test data was not available for our VCFS subjects, it would be informative to confirm these results and look for correlations with cognitive measures in VCFS in a larger set of subjects.

References


Pérez-Iglesias, R., et al. “White Matter Tracts of Interest were Determined from the Results of Tract-Based Spatial Statistics (TBSS) (Described in Kikinis et al., Poster #74). TBSS was Used to Highlight Areas of FA Difference Between Groups (Fig. 1a), the Results of Which Were Co-Registered to an Atlas of Average FA Patterns Across Our Caselast, and to a Universal White Matter Atlas (I.e., the Montreal Neurological Institute Atlas) (Fig. 1b). The Atlas Was Then Used to Identify Which Tracts Were Likely Driving the FA Differences Between Groups. In the Left Parietal Lobe, the Cingulum, Superior Longitudinal Fasciculus (SLF; Not Including the Arcuate Portion), Inferior Longitudinal Fasciculus (ILF), and Inferior Fronto-occipital Fasciculus (IFOF) Were Implicated. In the Cerebellum, in Both Hemispheres, the Short Intracerebellar Fibers Were Identified Based on Kanaan et al., 2009.

Tractography: In 3D Slicer, Streamlined Tractography Was Performed on Each Fiber Bundle of Interest Using Manually Traced Regions of Interest (ROIs) and Exclusion Regions (Fig. 2). Most ROIs Were Seeded 10 Times, Each Time Seeding From a New Random Start Point Within the Selected Voxels. Exceptions Were the SLF and Cerebellum, Which Were Isotropically Seeded Once, Due to the Large Number of Tracts Produced From One Seeding Session. Tracts of Interest Were Isolated by Selecting for Tracts That Passed Through All ROIs and Did Not Pass Through Exclusion Regions. Fiber Bundles Often Required Minor Manual Edits. The Cingulum Could Not Be Tracked in Full, So It Was Tracked in Dorsal and Ventral Portions.

HC mean FA VCFS mean FA significance

<table>
<thead>
<tr>
<th>Tract</th>
<th>HC mean FA</th>
<th>VCFS mean FA</th>
<th>Significance</th>
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<tbody>
<tr>
<td>IFOF</td>
<td>0.493 +/- 0.030</td>
<td>0.460 +/- 0.010</td>
<td>p = 0.002 **</td>
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<tr>
<td>ILF</td>
<td>0.476 +/- 0.025</td>
<td>0.453 +/- 0.023</td>
<td>p = 0.064 +</td>
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<td>SLF</td>
<td>0.473 +/- 0.023</td>
<td>0.470 +/- 0.025</td>
<td>p = 0.815</td>
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<td>Dorsal cingulum</td>
<td>0.519 +/- 0.027</td>
<td>0.519 +/- 0.027</td>
<td>p = 0.958</td>
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<tr>
<td>Ventral cingulum</td>
<td>0.380 +/- 0.034</td>
<td>0.346 +/- 0.025</td>
<td>p = 0.028 *</td>
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<tr>
<td>L intracerebellar</td>
<td>0.294 +/- 0.023</td>
<td>0.288 +/- 0.013</td>
<td>p = 0.525</td>
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<td>R intracerebellar</td>
<td>0.500 +/- 0.024</td>
<td>0.282 +/- 0.018</td>
<td>p = 0.102 +</td>
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