Investigating Williams Syndrome with Diffusion Tensor Imaging

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Introduction

Williams Syndrome (WS) is a neurodevelopmental disorder caused by a 1.5Mb deletion encompassing the elastin gene at 7q11.23, resulting in a set of characteristic physical, cognitive, and behavioral symptoms. Individuals with WS typically exhibit mild mental retardation with a unique combination of cognitive strengths and weaknesses, such as excellent verbal short-term memory and poor visuospatial construction. These individuals also typically demonstrate excessive friendliness, anxiety, empathy, and sensitivity to loud noises. This combination of cognitive and behavioral strengths and weaknesses suggests that multiple functional networks within the brain may be affected in different ways. This study utilizes diffusion tensor imaging (DTI) to investigate the involvement of white matter, the physical connections between functional areas of the brain, in Williams Syndrome.

Methods

Subjects Anatomic and DTI data were collected for 6 subjects with WS (mean age = 24 years, 4 male, 2 female, 4 right-handed and 2 left-handed) and 6 normal controls (CO) (mean age = 21 years, 3 male, 3 female, 6 right-handed). Anatomic data from a 7th CO was used as the target for image co-registration (age = 19 years, male, right-handed).

Image Acquisition Images were acquired with a 3T Philips Intera Achieva MR scanner with an 8-channel sensitivity encoding (SENSE) head coil and 80 mT/m gradients (100mT/m/ms slew-rate). For each subject, a 3D T1-weighted anatomic volume was obtained with a turbo field echo (TFE) sequence with matrix size of 256 x 256 x 170 and voxel size of 1mm^3. DTIs were obtained with a single-shot SE EPI sequence, using 32 diffusion encoding directions, tr(b) = 1000 s/mm^s, reconstructed matrix size of 128 x 128, 60 slices, and 2mm isotropic voxels.

Image Processing The DTIs were corrected for motion and image distortion with the Philips PRIDE Diffusion Registration tool prior to tensor calculation. Outlier rejection was also employed during the tensor calculation. Fractional anisotropy (FA), axial diffusivity ($\lambda_\parallel$) and radial diffusivity ($\lambda_\perp$) maps were calculated from the tensors. The parameter maps for each subject were co-registered to a common image space (the T1 volume of the target CO) using a multi-step intra- and inter-subject registration process, which involved the creation of an average FA template, to which the individual FA maps were then co-registered [1-3]. The image transformations created in this process were also applied to the diffusivity maps.

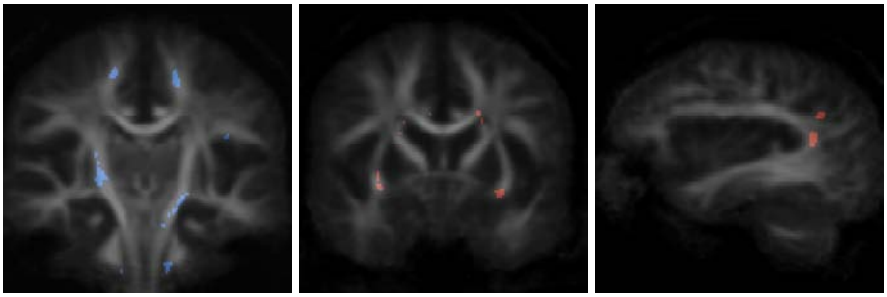
Group Comparison A voxel-wise student's t-test was performed on the co-registered parameter maps to compare the FA, $\lambda_\parallel$, and $\lambda_\perp$ values of the two groups. Because this was an exploratory study, the parameter maps were not smoothed (the extent of potentially affected areas is unknown [4]) and the statistical maps were not corrected for multiple comparisons (false positives were preferable to false negatives at this early stage).

Results

Significant differences ($p<0.005$) were found bilaterally in 4 regions of WM: the posterior limb of the internal capsule (IC), the corona radiata (CR), the superior longitudinal fasciculus (SLF), and the external capsule (EC). Both FA and $\lambda_\parallel$ were decreased in the WS subjects compared to the COs in the right and left IC and right and left CR, and $\lambda_\perp$ was increased in all of these regions, except in the left IC. FA was increased in the WS subjects compared to the COs in the right and left SLF and right and left EC; $\lambda_\parallel$ was also increased in all of these regions, except in the right SLF; and $\lambda_\perp$ was decreased in all of these regions, except for the left IC. These results are summarized in the table below.

Discussion

In this study, localized differences in FA, $\lambda_\parallel$, and $\lambda_\perp$ within the WM were observed in WS subjects when compared to COs. The combinations of decreased FA with decreased $\lambda_\parallel$ and increased $\lambda_\perp$ and increased FA with increased $\lambda_\parallel$ and decreased $\lambda_\perp$ suggest that the differences may be due to changes in axonal density or organization, not demyelination [5]. Increases in axonal density or organization in the SLF and EC may be related to the enhanced verbal abilities and startle reflexes exhibited by these subjects. Whereas decreases in axonal density or organization in the IC and CR could potentially be associated with deficits in fine motor control and visuospatial processing. Further investigation with additional data is needed to investigate the potential relationships between these changes in WM diffusion properties and function in WS.



Significant differences ($p<0.005$) in FA in WS subjects compared to CO subjects displayed on the average FA map. Left: Decreased FA (blue) in WS in the IC and CR. Center: Increased FA (red) in WS in the EC. Right: Increased FA (red) in WS in the left SLF.

WS compared to CO

	FA	$\lambda_\parallel$	$\lambda_\perp$
R Internal Capsule	↓	↓	↑
L Internal Capsule	↓	↓	-
R Corona Radiata	↓	↓	↑
L Corona Radiata	↓	↓	↑
R Superior Long. Fasc.	↑	-	↓
L Superior Long. Fasc.	↑	↑	↓
R External Capsule	↑	↑	↓
L External Capsule	↑	↑	↓

Right (R), Left (L), increased (↑), decreased (↓), and no change (-)

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