

Axonal Integrity of Brain White Matter Tracts in 22q11del Syndrome Subjects: A Diffusion Tensor Imaging Study

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BACKGROUND

Subjects with 22q11del syndrome are at high risk to develop schizophrenia; their incidence rate for developing the disease in adulthood is 30%, while the rate for the general population is 0.5% (Horowitz 2005). Several genes for which variations in nucleotide sequence are associated with schizophrenia are found in the 22q11del deletion site (Basset 2003).

Subjects with schizophrenia have been widely found to have reduced white matter fractional anisotropy (FA) (Assaf 2008). Other anisotropic measures such as radial and axial diffusivity have been shown to correspond to specific types of white matter damage in animal models.

The VCFS subjects examined in this study have also been found to have reduced white matter FA in the cerebellum on both sides and in the deep white matter of the parietal lobe in the left hemisphere. Here we are analyzing the same subjects for the anisotropic measures radial and axial diffusivity.

MATERIALS AND METHODS

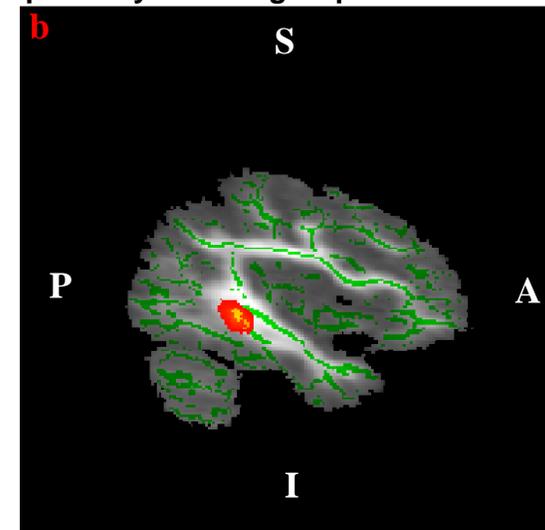
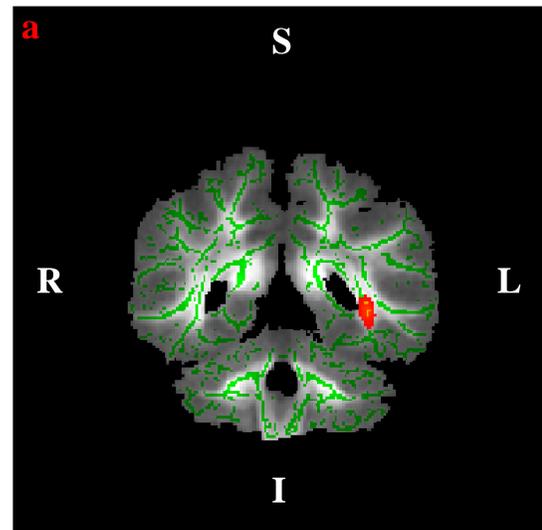
1.5T diffusion weighted scans were acquired from 9 patients with reconfirmed chromosomal deletion of region 22q11 and from 9 healthy subjects matched on age, sex, and parental socioeconomic status. Voxel-wise statistical analysis of various anisotropic diffusion measures was carried out using TBSS (Tract-Based Spatial Statistics) (Smith 2006).

First, brain-masked tensor map images were produced and anisotropic measures calculated with Slicer 3, an open source software program (<http://www.slicer3.org>). All subjects' FA images were then nonlinearly aligned into a common space. Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. At this point each subject's anisotropic data could be projected onto this common skeleton, and voxel-wise comparisons of the various anisotropic measures performed.

The permutation-based inference tool Randomize was used and a two sample *t*-test was conducted for all voxel-wise group comparisons using a threshold-free cluster enhancement method. The number of permutations was set at 500, and the significance level was set at Family-Wise Error (FWE) corrected $p < 0.05$. The tracts of the regions of reduction were identified by using John Hopkins University White-Matter Tractography Atlas.

RESULTS

Three views of FA reduction in 22q11del syndrome group



Reduction in Axial diffusivity

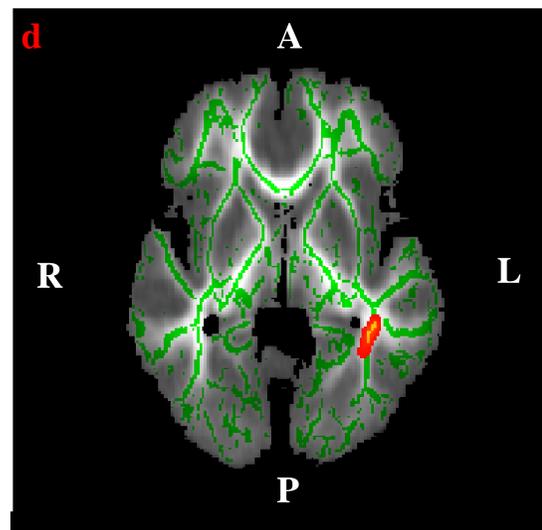
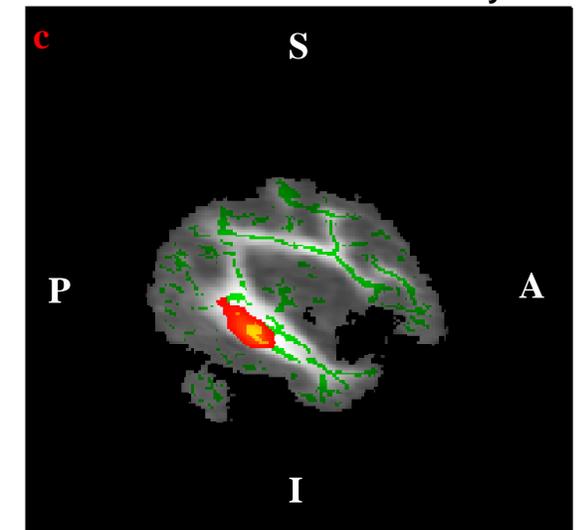


Figure: Thresholded mean FA image shown in grey, an average of all 18 brains in the study. Green lines represent the FA skeleton, the region calculated to be common to all brains. Reductions in anisotropic measures in the 22q11del syndrome group are shown in red-orange, where orange shows greater differences.

Significant reduction in axial diffusivity was found in the 22q11del syndrome group. Previous FA results showed an area of deep white matter in the parietal lobe in the left hemisphere for statistically significant reductions of FA in the 22q11del group (a, b, and d show three views of this region). The location of these white matter differences corresponds very closely to the reductions in axial diffusivity in the 22q11del group (c), a region of the parietal lobe which has several white matter tracts: the posterior thalamic radiation, inferior frontal occipital fasciculus (IFOF) and inferior longitudinal fasciculus (ILF). However, no similar difference in axial diffusivity was found to correspond with the FA differences in the cerebellum on both sides (not visible from the views shown in a, b, and d). No significant differences between the groups were found in the other anisotropic diffusion measure studied radial diffusivity.

DISCUSSION

Demyelination has been shown to result in increases in radial diffusivity in animal models (Kim 2006), while decreases in axial diffusivity are likely due to axonal damage (Song 2002). Our results suggest that axonal damage may be partially responsible for the reduced FA in these locations among the 22q11del group. Since radial diffusivity did not significantly increase, evidence of demyelination is not observed, and thus likely not involved in the white matter pathology of this disorder.

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