Anatomical Phenotyping of a Mouse Model with Known White Matter Abnormalities

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Introduction – Anatomical phenotyping in mouse models has shown to be quite useful for determining small specific changes in volume (1). Similarly, Diffusion Tensor Imaging (DTI) of fixed mouse brain has been useful in examining both development (2,3) and genetic differences between wild type and knockout mouse models (4). The purpose of this study was to determine both the volume and white matter structural changes in a mouse model with known white matter abnormalities, the Intersectin1 knockout mouse.

Methods – 24(14 for DTI) fixed mice brains were examined, 12(7) wild-type (WT) and 12(7) Intersectin1 knockout mice. *MRI Acquisition* – A multi-channel 7.0 Tesla MRI scanner (Varian Inc., Palo Alto, CA) with a 6-cm inner bore diameter insert gradient set (max gradient strength 100 G/cm) was used to all images of brains within skulls. 3 custom-built solenoid coils were used to image 3 brains in parallel. Parameters used in the anatomical conventional MRI scans: a T2- weighted, 3-D fast spin-echo sequence, with a TR of 325 ms, and TEs of 10 ms per echo for 6 echos, four averages, field-of-view of 14 × 14 × 25 mm^3 and matrix size = 432 × 432 × 780 giving an image with 0.032 mm isotropic voxels. Total imaging time was ~11 h. For the additional 3-D diffusion weighted fast spin-echo sequence an echo train length of 6 was used with a TR of 325 ms, first TE of 30 ms, and a TE of 6 ms for the remaining 5 echos, ten averages, field-of-view 14 x 14 x 25 mm^3 and a matrix size of 120, 120, 214 yielding an image with 0.117 mm isotropic voxels. One b=0 s/mm^2 image (with minimal diffusion weighting) and 6 high b-value images (b=1956 s/mm^2) in six different directions [(1,1,0),(1,0,1),(0,1,1),(-1,1,0),(-1,0,1),(0,1,-1)] (G_x,G_y,G_z). Total imaging time was ~16 hours. *Data Analysis* – To visualize and compare the volumetric and white matter structural changes, the brains for each MR sequence were registered together. For the volume measurements the registration resulted in deformation fields for each individual brain, which were used to calculate individual volumes from the segmented population average. For the white matter structural changes the intensity differences were assessed in a voxel by voxel basis for the white matter in the Fractional Anisotropy (FA) maps.

Results and Discussion – Sixty-two individual volumes were calculated for both the wild type and the Intersectin1 knockout mouse (5). Significant volume changes were found in 18 different regions. Some of the more notable regional differences were significant decreases in the anterior commisure (25%), corpus callosum (14%), and fimbria (23%), and a significant increase in the fourth ventricle (21%). The mean FA in the 62 different regions were also calculated; notable significant decreases in the intersection 1 FA were also found when compared to the wild type mouse in the anterior commisure (from 0.76 ± 0.04 to 0.54 ± 0.04), corpus callosum (from 0.75 ± 0.04 to 0.63 ± 0.02) and fimbria (from 0.90 ± 0.02 to 0.75 ± 0.02), which would correspond to the decreases in volume for those regions. No change in FA was found in the forth ventricle (0.29 ± 0.02 in WT and 0.29 ± 0.02 in Intersectin1 knockout), which is to be expected from a ventricle in the brain where there is no white or gray matter structure. Significant changes were also found with FA, where there were no specific volume changes. The arbor vita of the cerebellum showed no decrease in volume; however a decrease in FA, 0.72 ± 0.03 in the WT and 0.68 ± 0.02 in the Intersectin1 knockout. Figure 1, displays the FA decreases (top row) and volume changes (bottom row) for the Intersectin1 knockout mouse compared with WT.

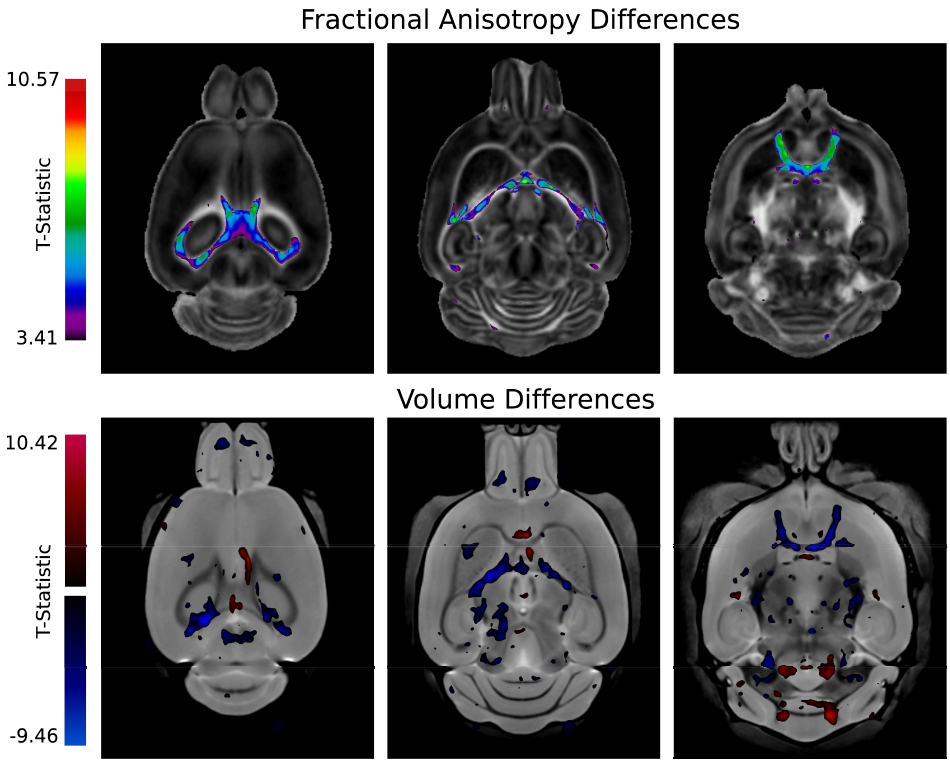

Figure 1 – **Top Row** – Significant Fractional Anisotropy (FA) decreases in the Intersectin1 knockout mouse when compared to wild type mice in specific white matter structures. From left to right the corpus callosum, fornix/fimbria, and anterior commisure all show significant decreases in FA. **Bottom Row** – Significant volume changes in the Intersectin1 knockout mouse when compared to wild type mice. Changes highlighted in blue indicate decreases, and changes indicated in red indicate increases.

Conclusions - While it is clear that some of the changes in FA are due to corresponding decreases in the volume (Figure 1), notably the anterior commisure, corpus callosum, and fimbira, some structures and regions have changes that would go unnoticed if only one of the methods was performed such as the fourth ventricle and arbor vita of the cerebellum.

References - 1) Nieman et al. *Physiol Genomics* 24: 154-162 (2006), 2) Mori et al. *MRM* 46:18-23 (2001), 3) Baloch et al. *Cerebral Cortex* Epub (2008), 4) Wang et al. J of Neurocience 26:355-364 (2006), 5) Dorr et al. *Neuroimage* 42:60-69 (2008)