A tract-based spatial statistics study of white matter compromise in pediatric brain tumor patients treated with cranial radiation

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Introduction and Purpose: Treatment with cranial-spinal radiation (CRT) is often required for effective control of aggressive pediatric brain tumours, such as medulloblastoma. Unfortunately, this modality is consistently associated with adverse late effects. White matter damage is the most striking anatomical change following CRT. Clinically it is documented as T2 hyper-intensity. Based on recent studies, changes in normal appearing white matter are also evident in children treated with CRT, including decreases in white matter volume. Diffusion Tensor Imaging (DTI) indices of white matter integrity in this population typically show increased mean diffusivity and decreased anisotropy relative to normal control children. More recently, there has been investigation of potential regional effects of CRT on white matter. Relatively greater decreases in white matter volume and Fractionated Anisotropy (FA) within frontal regions have been identified, suggesting greater radio sensitivity of these regions. These studies have not examined differences in FA across the whole brain in voxelwise manner, however. We examined differences in FA for children treated with CRT relative to control subjects using tract-based spatial statistics (TBSS) [1] to determine whether these differences are diffusely present across all regions of the brain or localized to specific regions.

Subjects and Methods: Seven patients treated with CRT for medulloblastoma (mean age = 9.98) and 7 control children (mean age = 9.84) participated in the study. Mean time from diagnosis to imaging was 2.50 ± .72 years. Data was acquired with a GE LX 1.5T MRI scanner using a single shot spin echo DTI sequence with an EPI readout (25 directions, TE/TR=100/6000ms, 128 x 128 matrix, FOV = 24 cm, rbw = 125 kHz). The number of slices and thickness varied across subjects as clinically required: 21 to 42 contiguous axial slices were acquired, and slice thickness ranged from 3 to 5.5mm across subjects. FA maps were created and non-linearly aligned to standard space (FMRIB58_FA) using TBSS. Using TBSS pre-processing, a skeletonized version of each FA map was created across subjects (Figure 1). Only those regions common to all subjects are considered for voxelwise analysis using a patient-control unpaired t test, with clusters defined by $t > 3$. The null distribution of the cluster-size statistic was built up over 5000 permutations of group membership.

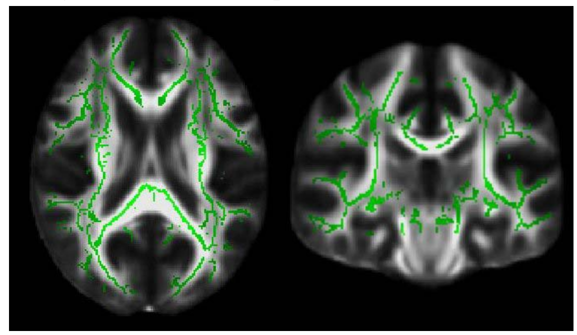

Figure 1. Mean FA skeleton of the 14 subjects overlaid on the FMRIB58_FA standard map.

Results: We identified reduced FA in patients treated with CRT relative to healthy controls across multiple regions, including the corpus callosum, internal capsule, cortico-spinal tracts, and hemisphere white matter, $p < .01$ (Figure 2).

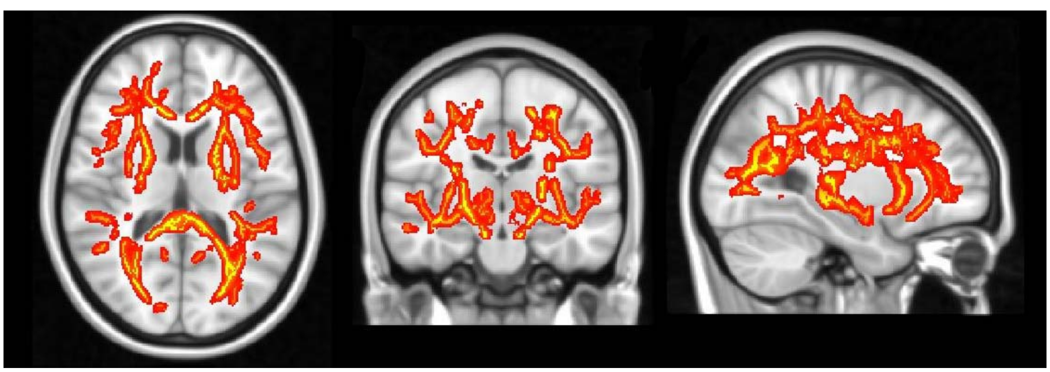

Figure 2. Regions of skeleton with significantly reduced FA for patients treated with CRT versus controls, overlaid on MNI avg152 brain. Skeleton width has been expanded for emphasis.

Conclusions: Using a tract-based spatial statistics methodology, we documented compromised white matter integrity in patients treated with CRT relative to controls. These differences were diffuse and there was no evidence of regional variation in FA differences between patients and controls. Patients in the present sample were seen for DTI imaging 2.50 years following treatment. It may be that regional variation in FA emerges over time. In future studies we will examine the impact of time since diagnosis on voxelwise evaluation of white matter integrity in patients treated with CRT. Regardless, the diffuse nature of compromise we identified in normal appearing white matter following treatment with CRT is striking.

References: [1] Smith et al (2006), Neuroimage, 31, 1487-1505.