White Matter Integrity Measured By Fractional Anisotropy Is Associated With Reading Ability In Pediatric Brain Tumor Patients: A Voxel Based Analysis Study Of Cognitive Outcome

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PURPOSE: Previous literature has established a decline in reading ability as well as damage to the white matter of the brain among patients treated for brain tumors diagnosed in childhood[1-2]. The purpose of this study is to examine the relationship between reading ability and white matter integrity among patients treated with cranial radiation and high dose chemotherapy for pediatric medulloblastoma/PNET, atypical rhabdoid tumor, or pineoblastoma.

PATIENTS AND METHODS: The study included 54 patients, ranging in age from 4.1 to 20.3 years at diagnosis (median=9.16 years), treated for infratentorial brain tumors with post-surgical risk-adapted craniospinal irradiation (CSI) and high-dose chemotherapy: High risk (HR, n=15) patients received CSI to 36-39.6 Gy and conformal boost treatment of the primary site to 55.8-59.4 Gy. Average-risk (AR, n=39) patients received CSI to 23.4 Gy, conformal boost treatment of the posterior fossa to 36 Gy and primary site to 55.8 Gy. Following treatment, all patients completed a neuropsychology evaluation at 12 months post-diagnosis, including measures of reading ability (Word Attack, Letter Word Identification, and Basic Reading Skills composite score) using the Woodcock Johnson Tests of Academic Achievement (Third Edition).

Patients also received a magnetic resonance imaging study at 12 months post-diagnosis. MR imaging was performed on a 1.5T whole-body system (Siemens Medical Systems, Iselin, NJ). Diffusion tensor imaging was acquired using bipolar diffusion-encoding gradients to reduce gradient-induced eddy currents that cause image distortion and degradation. All images were acquired as forty 3 mm thick contiguous sections with whole-head coverage and a 128 square matrix using a double spin echo EPI pulse sequence (TR/TE = 10/100 ms, b=1000 ms). Seven images, one in which b=0 and the others in which b=1000 s/mm^2, are used to calculate the diffusion tensor for each voxel. For the b=1000 images, the diffusion gradients were applied along non-collinear, non-coplanar directions in space. The set of images were acquired four times. Once the tensors have been calculated, Eigen values were derived and used to calculate fractional anisotropy (FA) maps.

Voxel-based analysis (VBA) began with registration of each original b=0 image to the ICBM average 152 T2 atlas aligned in Talairach space found in SPM2, resampled to a 1mm isotropic resolution. Registration consisted of a two-step process involving an affine transformation followed by a free-form deformation non-linear transformation which corrects for global brain shape differences, and were applied to the corresponding FA maps. A white matter mask was created by segmenting the T2 atlas using SPM2. A voxel-based analysis of variance (ANOVA) was performed using SPM2 to identify regions with an association between FA and Word Attack scores, controlling for age at examination, within the white matter mask. P-value and cluster thresholds were specified to limit the analysis only to regions that have significant differences and have a sufficient number of continuous voxels for analysis.

RESULTS: Two clusters in the temporal-parietal region were identified by the VBA. The first in the left was 77 mm^3 in size, and the second in the right was 80 mm^3 in size. The respective Talairach coordinates were (-18 -24 -8) and (18 -14 -10) (**Figure 1**). Regression models, controlling for age at treatment and risk arm, revealed a significant relationship between these regions and the reading scores (**Table 1**).

Figure 1. VBA clusters identified in the left and right temporal-parietal regions. Images are displayed on the average FA map calculated from all 54 subjects in the study after normalization.

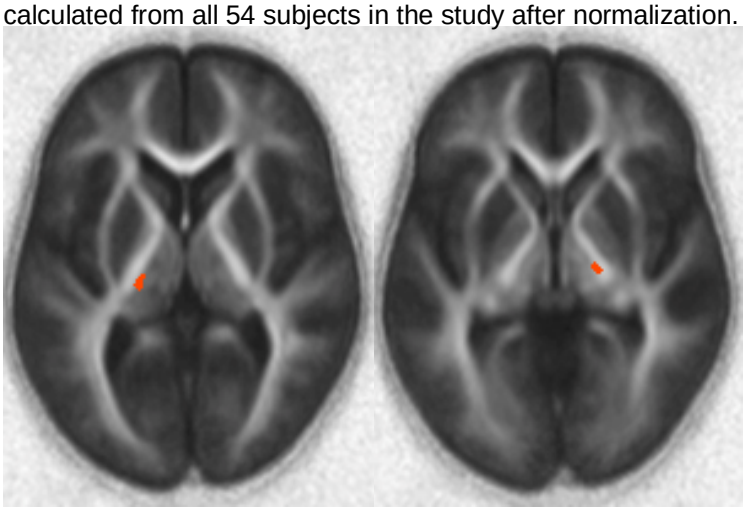

Table 1. Results of regression models for reading measures and FA scores, controlling for age at enrollment and diagnosed risk (Average vs. High).

	Left FA	Right FA
Word Attack	R=0.338 (p=0.020)	R=0.458 (p=0.001)
Letter Word ID	R=0.257 (p=0.081)	R=0.397 (p=0.006)
Basic Reading	R=0.318 (p=0.030)	R=0.442 (p=0.002)

CONCLUSIONS: Fractional anisotropy measures the directional organization of water diffusion within a region and reflects the integrity of white matter microstructure. The integrity of the microstructure in the two regions of interest may contribute to the patient's reading ability by strengthening communication between visual, auditory, and language cortical areas. Specific attention to these areas of the brain during radiation treatment planning may be necessary to reduce treatment related deficits.

REFERENCE: [1] Mulhern RK et al. JCO, 23:5511-9, 2005. [2] Reddick WE et al. Neuro Onc, 7:12-9, 2005.