Improve Myelin Imaging Biomarkers Specificity by Modeling Extra-cellular Tissue Water

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Target Audience: This work is for those who are interested in employing diffusion MRI, and magnetization transfer ratio (MTR) as demyelination biomarkers for CNS diseases.

Purpose: Myelin damage is common in CNS diseases. Imaging biomarker specific to myelin integrity is desired to reflect myelin damage, and monitor efficacy of remyelination therapies. Radial diffusivity (RD) derived by diffusion tenor imaging (DTI) and magnetization transfer ratio (MTR) are known sensitive to myelin integrity.[1-3] However, the specificity of DTI and MTR to myelin integrity is confounded by other coexisting pathologies.[1,4-7] In this study, we conducted both myelin quantification using histology analysis and diffusion MRI on MS spinal cord specimens to examine the role of extra-cellular tissue water on the specificity of myelin imaging biomarkers. We also extended our findings to diffusion MRI and MTR data of MS patients.

Method: Autopsied MS spinal cord specimens: Cervical spinal cord specimens were obtained following autopsy from three MS patients. Post-mortem time until autopsy was within 10 hours. The spinal cord tissues were fixed in 10% formalin in phosphate buffered saline (PBS) at room temperature after autopsy. Ex vivo MRI: MS spinal cords were examined using an Agilent 4.7 T magnet, actively shielded Magnex gradient coil (60 G/cm). Data acquisition uses repetition time (TR) 2s, echo time (TE) 39 ms, diffusion time 17 ms. Diffusion gradients were applied in 99 directions with max b-value = 3200 s/mm^2. Voxel size=250x250 μm^2. Histology: The spinal cord specimens were embedded in paraffin and sectioned at 5-μm thick. Sections were individually stained with Luxol Fast Blue-Periodic Acid Schiff (LFB-PAS) stains for myelin. Images were acquired with a NanoZoomer 2.0-HT System (Hamamatsu, Japan) using a 40× objectives. The raw histology image was down-sampled and co-registered to MR images. 89 regions of interest (ROIs) were randomly selected on registered images. Positive myelin stains was manually counted. The fraction of myelin area was computed. Human Subjects: Procedures involving human subjects were approved by the Institutional Review Board of Washington University. Three MS patients provided informed consent. Forty two ROIs were manually delineated to include regions with MTR values from 0.04 to 0.4, representing lesions of "black holes" in T1-weighted images to normal appearing white matter in the corpus callosum.

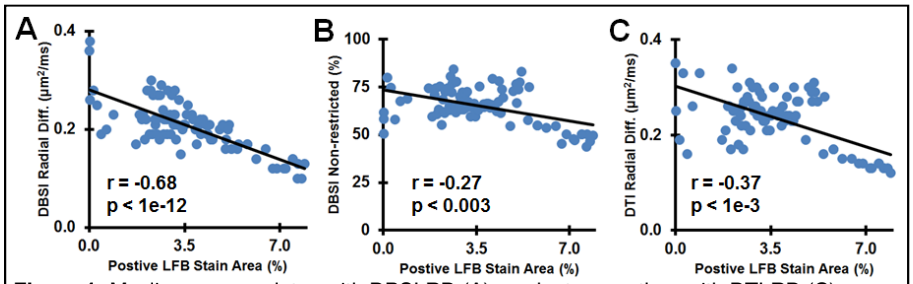

Figure 1: Myelin area correlates with DBSI RD (A) much stronger than with DTI RD (C). Myelin area weakly correlates with DBSI non-restricted isotropic fraction (B), probably reflecting the inflammatory demyelinating nature of the MS.

Human MRI: A 3-Tesla TIM Trio scanner with a 32-channel head coil (Siemens, Erlangen, Germany) was employed. Diffusion MRI data were collected at 2x2x2 mm^3 resolution with TR/TE = 10000/120ms. The max b-value was 2000 s/mm^2. The 99-direction diffusion scheme was employed and the total acquisition time was 15 minutes. Standard MTR sequence on Siemens scanner was used to generate MTR images.

DBSI/DTI Analysis: Diffusion basis spectrum imaging (DBSI) has recently been developed and validated to differentiate and quantify axonal injury/loss, demyelination, and inflammation.[8-10] Previous study has shown that DBSI can distinguish demyelination from edema in tissue phantoms and Monte-Carlo simulations.[9] Conventional DTI was also computed. Statistical Analysis: Spearman's rank correlation coefficients were used to measure the strength of monotone association between diffusion MRI metrics and positive myelin fraction. The correlation between MTR and diffusion MRI metrics on all ROIs for MS patients was also similarly examined using Spears's rank correlation.

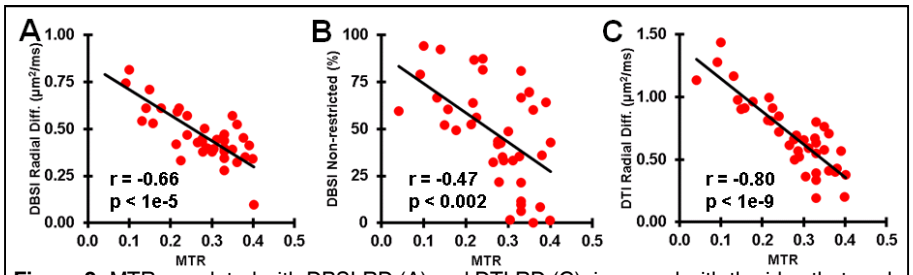

Figure 2: MTR correlated with DBSI RD (A) and DTI RD (C), in accord with the idea that each of these three imaging biomarkers is sensitive to myelin integrity. MTR correlated with DBSI non-restricted isotropic fraction (B), suggesting that MTR is also sensitive to increased tissue water content, likely edema and/or tissue loss.

Results and Discussion: Myelin area correlated much better (r=-0.68, p<1e-12 Fig. 1A) with DBSI RD than with DTI RD (r=-0.37, p<1e-3 Fig.1C). DBSI RD and DBSI non-restricted isotropic diffusion fraction (reflecting extra-cellular tissue water) both correlated with DTI RD (r=0.51, p<1e-6, and r=0.59, p<1e-9 respectively), consistent with previous finding that DTI RD increases with demyelination and increased tissue water.[8-10] Myelin area weakly correlated with DBSI non-restricted isotropic diffusion fraction (r=-0.27, p<0003 Fig. 1B), probably reflecting the inflammatory demyelinating nature of the MS. The data clearly suggested that DBSI significantly improved the specificity of RD to reflect myelin integrity by distinguishing and quantifying the effect of extra-cellular tissue water. For diffusion MRI and MTR measures from MS patients, MTR correlated with both DBSI RD (Fig. 2 A; r = -0.66, p <1e-5) and DBSI non-restricted isotropic diffusion fraction (r = -0.47, p<0.002) (Fig. 2B), in accord with prior studies showing that MTR reduction is not only associated with demyelination but also is sensitive to increased tissue water content.[2,6,7] Strongest correlation was found between MTR and DTI RD (Fig. 2 C; r = -0.80; p<1e-9), suggesting that both MTR and DTI reflected demyelination and co-existing extra-cellular tissue water in MS.

Conclusion: DTI RD and MTR were affected by both myelin integrity and tissue water. By modeling both anisotropic and isotropic diffusion components, DBSI provided a novel biomarker more specific to myelin (DBSI RD) and a unique biomarker of tissue water (DBSI non-restricted isotropic fraction).

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