Using MR frequency shifts to differentiate MS lesion pathologies

Vanessa Wiggermann[1,2], Samantha Y.Y. Tan[3], Enedino Hernández Torres[1,4], David K.B. Li[1,4], Alex L. MacKay[2,4], Irene M. Vavasour[1,4], Nicholas Seneca[5], David Leppert[5], Shannon Kolind[4,6], Anthony Traboulsee[4,6], and Alexander Rauscher[1,4]

[1]Radiology, University of British Columbia, Vancouver, BC, Canada, [2]Physics and Astronomy, University of British Columbia, Vancouver, BC, Canada, [3]Science, University of British Columbia, Vancouver, BC, Canada, [4]UBC MRI Research Centre, Vancouver, BC, Canada, [5]F. Hoffmann-La Roche Ltd., Basel, Switzerland, [6]Neurology, University of British Columbia, Vancouver, BC, Canada

Target Audience: Clinicians, Radiologist, MR researchers, basic scientists

Purpose: Multiple sclerosis (MS) is characterized by episodic inflammation in focal lesions resulting in demyelination of axons, astrocytic scarring, progressive neurodegeneration, remyelination and axonal injury, all to a highly variable degree. Conventional MR outcomes correlate poorly with the patient's clinical status[1]; this discrepancy might be associated with the failure of current MR imaging techniques to quantify the heterogeneity of focal lesion pathology. High-resolution MR frequency shift imaging has been shown to be sensitive to the myelin state[2-4] and offers the possibility to improve the monitoring of patients. The sensitivity of MR frequency shifts to myelin and axonal loss[5] could improve the discrimination of the severity of MS lesion pathology. The goal of this study was to compare MR frequency shifts in three different types of lesions to myelin-related MR metrics: magnetization transfer ratio (MTR) and myelin water fraction (MWF).

Methods: 25 subjects with relapsing-remitting MS (age range: 21-54 years; median expanded disability status scale (EDSS) = 2) participating in a phase III randomized active-controlled clinical trial of ocreluzimab were scanned at baseline before treatment initiation. MR frequency shift maps were calculated from the gradient echo acquisition (6 echoes, TR/TE/ΔTE =38/4/4.5ms, reconstructed voxel-size: 0.5 x 0.5x1mm^3), using Laplacian phase unwrapping[6], followed by weak high-pass filtering in 2D using a Gaussian kernel with sigma of 9 pixels. A single echo at 22ms was chosen for analysis. Also, magnetization transfer[7] and myelin water[8] images were acquired in addition to the conventional FLuid Attenuated Inversion Recovery (FLAIR) and T1-gadolinium (Gd) enhanced sequences. All scans were registered to the frequency images and regions of interest in MS lesions were defined manually on FLAIR scans. The average frequency shifts, MTR and MWF values were computed for each lesion. Kruskal-Wallis and Wilcoxon Rank sum tests were performed to evaluate group differences.

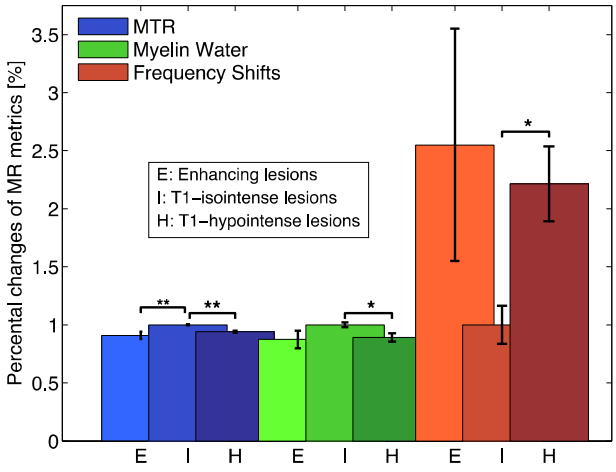

Fig. 1: Mean values and standard errors for the three metrics. (* - p<0.01, ** - p<0.001)

Results: Of the 738 lesions identified, 16 were Gd-enhancing lesions (E), 583 were T2-hyperintense/T1-isointense (I) and 139 were T2-hyperintense/T1-hypointense (H). Fig. 1 shows the mean values and standard errors for each metric by lesion type. T1-hypointense lesions differed significantly (p<0.01) from T1-isointense lesions for all three techniques, but frequency shift showed a much larger mean difference (121%) between lesion types than MTR (6%) or MWF (10%). Unlike MTR or MWF, frequency shifts varied strongly between individual enhancing lesions. However, MTR was the only metric to significantly differentiate enhancing and isointense lesions (9%, p=0.001).

Discussion: Frequency shifts showed large differences between T1-isointense and other lesions and varied strongly within lesion subtypes. The observed trends seem to agree with theoretical predictions of frequency shifts at different stages of demyelination and axonal loss[5] and with experimental results that show a steep increase in frequency around the time of Gd-enhancement[3]. MTR and MWF are more established markers for myelin. However, MTR is influenced by inflammation and edema, and MWF is noisier and has lower spatial resolution. Note that none of these advanced measures distinguished enhancing from T1-hypointense lesions.

Conclusions: Within lesions types, frequency shifts show heterogeneity between individual lesions, whereas results obtained with MTR and MWF are very similar between lesions. Given the high SNR of frequency maps, this finding suggests that MR frequency provides information of lesion variability within subtypes, referring to changes of the myelin state as well as axonal loss.

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