Application of CEST Imaging to Study Amide Proton Transfer (APT) in Healthy Controls and Multiple Sclerosis Pathology at 7 Tesla

A. N. Dula[1,2], R. D. Dortch[1,2], B. A. Landman[2,3], S. Pawate[4], P. J. Lavin[4], E. B. Welch[1,5], J. C. Gore[1,2], and S. A. Smith[1,2]

[1]Vanderbilt Institute of Imaging Science, Vanderbilt University, Nashville, TN, United States, [2]Radiology and Radiological Sciences, Vanderbilt Medical Center, Nashville, TN, United States, [3]Electrical Engineering & Computer Science, Vanderbilt University, Nashville, TN, United States, [4]Neurology, Vanderbilt Medical Center, Nashville, TN, United States, [5]3MR Clinical Science, Philips Healthcare, Cleveland, OH, United States

INTRODUCTION The ability to obtain increased contrast from chemical exchange saturation transfer (CEST) effects in human brain at high field (7T) has been used to study amide proton transfer (APT) and applied in multiple sclerosis (MS). APT imaging, a relatively new contrast arising from examining specific resonance spectra in CEST imaging, is sensitive to the mobile protons associated with proteins and peptides. The increased signal, longitudinal relaxation time, and spectral dispersion at 7T presents an opportunity for application of this molecular MRI method. MRI is well established as the imaging modality for the diagnosis and monitoring of multiple sclerosis (MS). Improvements in sensitivity and spatial resolution with increasing field strengths have provided corresponding improvements in the conspicuity of early MS lesions.[1-3] With the recent introduction of 7T, there is reason to expect further improvement in sensitivity, as well as novel information regarding MS pathology *in vivo*.[4,5] Traditional MRI techniques used to evaluate MS lesions lack specificity and suffer from limitations at 7T. APT imaging has proven useful for evaluation of neoplasms, potentially differentiating between edema and tumor tissue,[6] however, it has not been applied to studying multiple sclerosis (perhaps due to the lack of contrast obtained at 3T). The purpose of this abstract is to use 7T APT asymmetry analysis to examine unique white matter (WM), gray matter (GM) contrast in healthy controls as well as a multiple sclerosis patient presenting with optic neuritis and tentorial lesions localized to the optic radiation. Herein, we utilize the Water Spectrum Shift Reference (WASSR) method to correct for B_0 inhomogeneities and center the CEST spectra.[7]

METHODS **Image acquisition** Six healthy controls and one patient were scanned using a Philips Achieva 7T with a 16 channel NOVA head coil for signal reception. A 3D FFE sequence with single-shot TFE and a SENSE factor of 2.5 (AP) was used resulting in 2.1 x 2.1 x 3.0 mm resolution with eight slices acquired. WASSR data were collected to correct the center frequency with the same volume using a 0.5 μT, 100 ms RF pulse at offsets between ± 300 Hz with a scan time of five minutes.[7] The CEST data were acquired using a 3.5 μT, 500 ms RF block pulse at 25 offsets between ± 1350 Hz with a scan time of nine minutes. In addition, T_1-weighted, T_2^*-weighted, and FLAIR images were acquired for comparison and region of interest (ROI) selection. The T_1-weighted and T_2^*-weighted scans were 0.5 x 0.5 3.0 mm resolution using 3D and 2D fast field echo techniques, respectively. The FLAIR data were 1.0 mm isotropic resolution as described by Zwanenburg et al.[8] **Image Analysis** The minima of WASSR z-spectra were calculated for each voxel and applied to the normalized CEST spectra.[7] ROIs were manually drawn based on the anatomical images and asymmetry was calculated for the amide resonance (3.5 ppm) using $CEST_{asym}(\Delta\omega) = \frac{S(-\Delta\omega) - S(\Delta\omega)}{S_o}$.

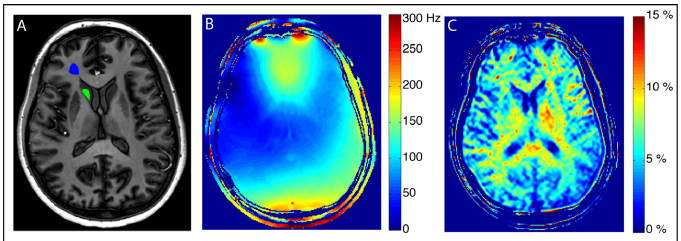

Fig 1 - A) Anatomical image with frontal white matter (blue) and caudate (green) outlined, B) Shift map derived using WASSR method, and C) Asymmetry map for amide resonance (3.5 ppm) with clear white/grey matter contrast.

RESULTS and DISCUSSION Anatomical, WASSR, and CEST images were successfully acquired on six healthy controls and one MS patient at 7T with a structural image (A), shift map (B), and asymmetry map (C) from a healthy control shown in Fig. 1. The calculated asymmetry map at the amide resonance (3.5 ppm) in Fig. 1C exhibits contrast between healthy tissue types, i.e. WM and GM. The appearance of structural delineation in the asymmetry map can be attributed to the increased signal, relative exchange rate, as well as spectral dispersion available at 7T providing increased sensitivity to the disparity of endogenous mobile proteins within these tissues. This novel WM/GM contrast was applied to the WM pathology in MS apparent in the optic radiation with results shown in Fig. 2. The lesion in the left optic radiation (arrow) appears hypointense on the T_1-weighted image (Fig. 2A) and hyperintense on both the T_2^*-weighted (Fig. 2B) and the FLAIR (Fig. 2C) images. The asymmetry map for 3.5 ppm is shown in Fig. 2D with increased asymmetry in the lesion as well as normal appearing WM. APT imaging at 7T probes endogenous mobile proteins and peptides, which are expected to vary among tissues. However neither contrast in the asymmetry maps between healthy tissue types, i.e. white matter (WM) and grey matter nor APT contrast in MS have been found at the lower field strengths of 1.5T or 3T. This contrast is further demonstrated using ROI analysis summarized in Fig. 3 with ROIs outlined in Figs 1A (healthy WM and GM) and 2A (lesion). The increase in asymmetry at the amide resonance in pathology can be partly attributed to a larger amount of endogenous mobile proteins and peptides associated with the breakdown of myelin and macrophage infiltration. Molecular examination of MS lesions at 7T using APT imaging could reveal novel information regarding the lesion type, age, prognosis, and efficacy of treatment.

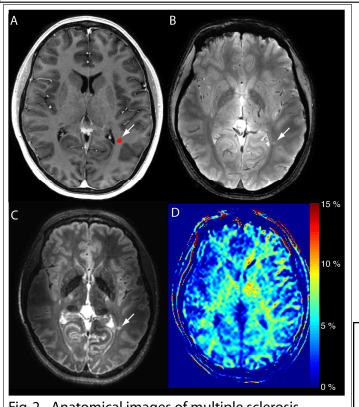

Fig. 2 - Anatomical images of multiple sclerosis patient at 7 Tesla. A) T1w scan with optic radiation lesion indicated by arrow and lesion ROI delineated coinciding with Fig. 3. B) T2*w scan with lesion appearing hyperintense and C) FLAIR image with lesion appearing hyperintense. D) Asymmetry map at the amide resonance (3.5 ppm).

REFERENCES **1**.Invest Radiol, 41(2):76. **2**.Invest Radiol, 38(7):423. **3**.Eur Radiol, 16(7):1494. **4**.Arch Neurol, 65(6): p812. **5**.Neurol, 70(22): p2076. **6**. MRM 56:585 **7.** MRM 61(6):1441 **8.** Eur. Radiol, Oct.3 (Epub)

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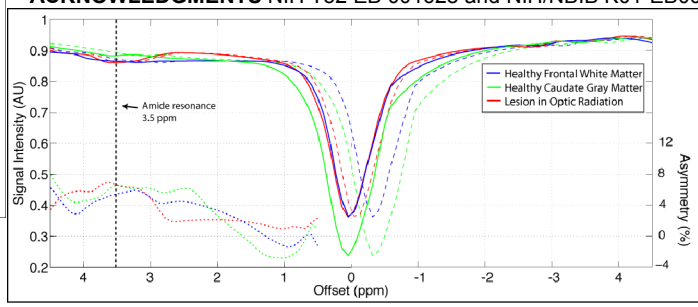

Fig. 3 - Region of interest analysis for healthy control and optic neuritis patient at 7T. Dashed lines indicate normalized z-spectra prior to centering from various regions of interest, healthy WM - blue, healthy caudate (GM) - green, and lesion in optic radiation - red. The solid lines indicate application of the WASSR shift. The inset dotted lines are the CEST asymmetry corresponding with the right side y-axis. The location of the amides is indicated by the dashed black line. The asymmetry of the lesion is increased at this resonance indicating an increase in the amide concentration.