Application of Chemical Exchange Saturation Transfer (CEST) Imaging to Examine Amide Proton Transfer (APT) in the Spinal Cord at 3T

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INTRODUCTION Multiple Sclerosis (MS) is a neurological condition affecting 600,000 adults in the U.S. alone (1) whose essential feature is white/gray matter lesions marked by inflammation, demyelination/axonal damage, and necrosis (2). Standard clinical imaging does not provide markers that reflect these processes specifically, particularly in the spinal cord where inflammation is often less pronounced. More advanced MRI methods have been developed to examine MS pathology based on water interactions with semi-solid macromolecular protons (sensitive to myelin content) or with barriers (sensitive to axon/myelin integrity or inflammation). Chemical exchange saturation transfer (CEST) imaging is sensitive solute/water proton exchange at specific offset frequencies, e.g. 3.5 ppm for amide protons (3), an effect that depends on several factors including pH. This sensitivity to tissue properties, such as the concentrations of the exchange partners and their rate of proton exchange, has been exploited in studies of healthy spinal cord at 3T (4) and MS pathology in the brain at 7T (5), but has not previously been applied to the diseased spinal cord. Here we use CEST to study the cervical spinal cord to establish variability in a normal population as well as an MS patient with known spinal cord lesions.

METHODS **Image acquisition** Five healthy controls and one MS patient (2/4 male/female), mean age 29, range 25-32, were scanned using a Philips Achieva 3T scanner (Philips Healthcare, Best, Netherlands). A 16 channel neurovascular coil was used for signal reception. A 3D gradient echo with single-shot turbo-field echo sequence and a SENSE factor of 2.5 (RL) was used to acquire 9 slices with 1.5x1.5x8.0mm^3 resolution. The CEST spectra were acquired using a 0.5 μT, 500 ms RF block pre-pulse at 33 offsets between ± 7.0 ppm, TR/TE/flip angle = 5.2ms/2.7ms/9° resulting in a scan time under nine minutes. In addition, T_2-weighted, and magnetization transfer-weighted (MT) images were acquired for comparison and region of interest (ROI) selection. The T_2-weighted scans were 1.0x1.0x4.0mm^3 resolution using 3D fast field echo acquisition. The MT data were 0.8x0.8x3.0mm^3 resolution achieved in four minutes using a multi-echo gradient echo PD/T2*w sequence including a 1-3-3-1 binomial pulse for fat suppression. **Image Analysis** The CEST data were rigidly registered slice-by-slice and normalized to the maximum signal intensity present in the S_0 image. The CEST z-spectra were interpolated to 500 points and fit to a 25th order polynomial in Matlab (Mathworks, Natick, MA). The minimum of this fit was assigned as the water frequency and the CEST spectra were shifted accordingly and extrapolated back to the acquired 33 saturation offset frequencies. The CEST spectra were examined as a function of saturation offset frequency according to: $CEST_{asym}(\Delta\omega) = \frac{S(-\Delta\omega) - S(\Delta\omega)}{S_o}$. and amide proton transfer asymmetry (APT_{asym}) was calculated for the amide resonance (3.5 ppm). ROIs were manually drawn based on the anatomical images. MT ratio (MTR) maps were also calculated.(6)

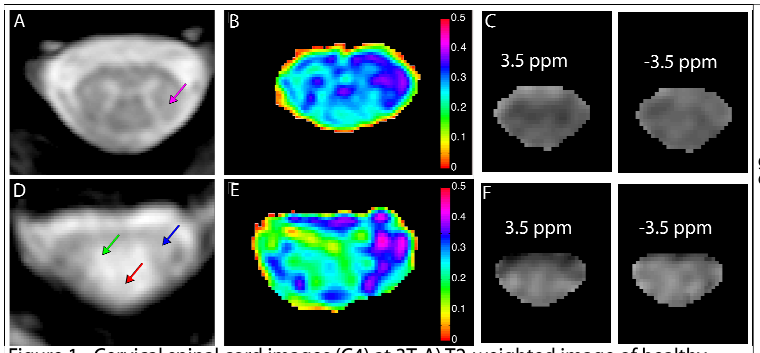

Figure 1 - Cervical spinal cord images (C4) at 3T. A) T2-weighted image of healthy control. B) MTR map of healthy control. C) S/S0 images from CEST data at +/- 3.5 ppm D) T2-weighted image of multiple sclerosis patient with arrows indicating normal appearing white matter (blue), gray matter (green), and lesion (red). E) Corresponding MTR map, and F) S/S0 images from CEST acquisition for both +/- 3.5 ppm.

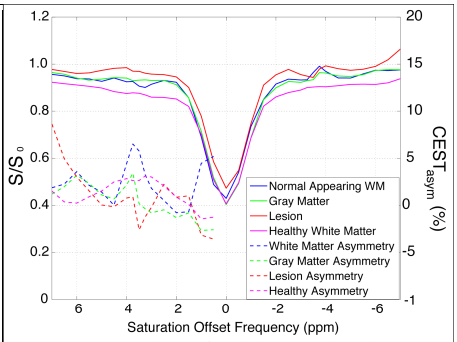

Figure 2 - ROI analysis of healthy control and MS patient at 3T. Solid lines indicate normalized and shifted z-spectra from various regions of interest as indicated by arrows in Fig. 1. Dashed lines represent the calculated CEST asymmetry (right y-axis).

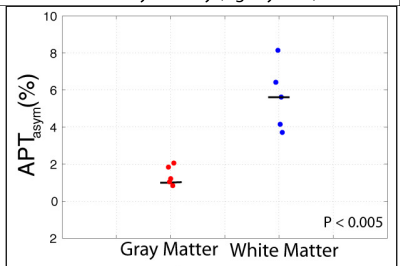

Figure 3 - Region of interest analysis on 3T spine data using CEST MRI to calculate amide proton transfer asymmetry (APTasym).

RESULTS & DISCUSSION Representative results from a healthy control (Fig.1A-B), and MS subject (Fig.1C-D) demonstrate white/gray matter contrast in both T_2 (A&D) and MTR (B&E) images. A white matter lesion in the dorsal column (red arrow) is apparent as a hyperintensity on the T_2-weighted image in Fig. 1D as well as a relative decrease in MTR in Fig. 1E. Panels C and F show the S/S_0 images from the CEST spectra. Region of interest analysis results are shown in Fig. 2, solid lines represent normalized and shifted CEST spectra from normal appearing white matter (blue), gray matter (green) and lesion (red) from MS subject as well as white matter from a control (magenta). APT_{asym} measures from the five healthy controls are shown in Fig. 3. The APT_{asym} was found to be significantly different between gray matter and white matter regions of interest. This difference can be attributed to difference in the exchange properties and concentrations of mobile amide protons in healthy gray/white matter in the spinal cord, detectable by the CEST MRI method implemented at 3T. These findings suggest a potential use for CEST MRI for characterization of MS spinal cord lesions.

Aknowledgements NIH T32 EB 001628 and NIH/NBIB K01-EB009120 **References** 1) Kaplin AI, et al., *Neurology*. 69(4):410. 2) Raine CS. *Ann. Neurol.* 1994;36:S61. 3) Zhou JY, et al., *Nat. Med.* 9(8):1085. 4) Ng MC, et al., *JMRI* 29:523-528. 5) Dula AN, et al., *ISMRM,* 2010. 6) Wolff SD, et al., *MRM* 10(1):135-144.