# Chemical Exchange Saturation Transfer (CEST) MRI as a Biomarker for Diffuse Pathology of Normal Appearing White Matter in the Brain and Spinal Cord in Multiple Sclerosis

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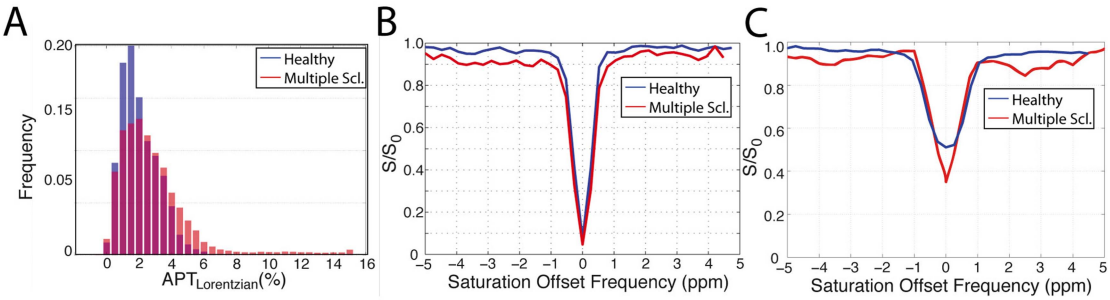
**Purpose:** A hallmark of multiple sclerosis (MS) is macroscopic discrete focal demyelinating lesions in the central white matter (WM) but other widespread abnormalities are known to exist in all subgroups of MS in both the brain and spinal cord (SC). Normal appearing WM (NAWM) exhibits subtle diffuse pathologies that may be present from disease onset.[1] While demyelination is not always evident, the NAWM exhibits: mild inflammation[1] causing increased cytokines and other mediators, leaky vessels infiltration of macrophages and adhesion molecules,[2] increased expression of proteolytic enzymes,[3] microglial activation, and axonal loss. The goal of this study was to evaluate the ability of MRI contrast due to chemical exchange by saturation transfer (CEST) to measure changes in composition via amide proton transfer (APT) effect in NAWM of the brain and SC in subjects with MS and compare values to those in healthy controls.

**Methods:** Imaging was performed on a Philips Achieva 7 T scanner (Philips Healthcare, Cleveland, OH) and was approved by our IRB. A 32-channel NOVA head coil (NOVA Medical, Wilmington, MA) was used for brain imaging while SC imaging used a surface quadrature transmit coil and a 16-channel receive spine array (Nova Medical). Six healthy controls and nine relapsing-remitting MS patients underwent 7 T CEST MRI of either the brain or SC. CEST saturation was achieved using a 25 ms windowed-Gauss pulse with 1 μT amplitude at a range of frequencies between ±5ppm along with an $\Delta\omega$ = 80 ppm acquired for normalization. *Data Processing*: Each slice at each offset frequency, $S(\Delta\omega)$, was non-rigidly co-registered and normalized to $S_0$. Voxel-wise data were fit to a single Lorentzian and minima of fits were used as the center water frequency ($\Delta\omega = 0$) and shifted accordingly. The CEST effects (APT) were calculated as the integrated area between the acquired data and the Lorentzian fit for 3ppm<$\Delta\omega$<4ppm, termed $APT_{Lorentzian}$. NAWM was manually segmented using a threshold method and histograms of NAWM APT metrics were compared between healthy and MS subjects.




**Results –** The figure demonstrates comprehensive results of CEST MRI on the brain (Panels A & B) and SC (Panel C) of healthy controls and MS patients. Panel A shows a histogram of the calculated $APT_{Lorentzian}$ in the brain NAWM for healthy controls (blue) and MS subjects (red), with overlap appearing in purple. The mean APT effect was significantly different ($p < 0.01$) for healthy (2.03 ± 1.14%) and MS subjects (2.91 ± 2.42%). Additionally, the MS data exhibits considerable positive skewness (2.49) to higher $APT_{Lorentzian}$ values relative to that of healthy subjects (0.79). This positive skewness of the MS APT measure is potentially reflective of the diffuse pathophysiology of the NAWM known to exist in MS. Panels B & C present representative spectra from WM from healthy controls and MS subjects, demonstrating the increase in the CEST effect around -3.5 ppm found in MS for both the brain (B) and SC (C).

**Discussion –** Using the Lorentzian fit for CEST quantification accounts for asymmetric magnetization transfer effects, lipid contamination, NOE, and baseline noise, all of which can confound conventional asymmetry calculations (see Panels B & C). The larger standard deviation found in APT measures in NAWM could be due to the known variation in pathological substrates based on proximity to WM lesions. Advance segmentation algorithims are under development to overcome this issue. Additionally, we hypothesize that the positive skewness of the MS APT distribution is potentially reflective of the diffuse pathophysiology of the NAWM known to exist in MS.

**Conclusion –** We have demonstrated the utility of CEST MRI for examination of NAWM white matter in MS patients. The NAWM is typically an understudied realm of MS, particularly in the spinal cord. We have applied CEST MRI at 7 T with results indicating a global increase in the measured APT metric in WM for MS subjects verses that of healthy controls. As the APT effect is thought to be related to the protein content of tissue, the presented results indicate CEST MRI could act as a biomarker for NAWM alterations in MS.

**References –** 1) Allen IV, McQuaid S, Mirakhur M, Nevin G. *Neurol Sciences.* 2001;22(2):141-144. 2) Matsuda M, Tsukada N, Miyagi K, Yanagisawa N. *J Neuroimmunol.* Jun 1995;59(1-2):35-40. 3) Ludwin SK. *J Neuropath Exp Neur.* Apr 2006;65(4):305-318.

**Aknowledgements -** NIH KL2 000446, K01 EB009120, EB000461