# Characterization of the optic nerve *in-vivo* using high-resolution APT-CEST

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**Target Audience:** Researchers and clinicians interested in quantitative MRI of the optic nerve and the White Matter Study Group of the ISMRM.

**Purpose:** To demonstrate high-resolution chemical exchange saturation transfer (CEST) of the optic nerve.

**Introduction:** Visual dysfunction is a hallmark of multiple sclerosis (MS) and may arise from damage (demyelination and axonal loss) to different components (e.g., optic nerve (ON), optic tract, and optic radiation) of the visual system, of which the ON is perhaps the most critical, because optic neuritis is often the presenting symptom in many cases of MS [1,2]. One challenge is to develop assessment strategies that can capture optic neuritis and relate changes of the ON to eventual development of MS. However, quantitative MRI is not typically employed in the ON due to its size (< 6mm) and location (proximal to the maxillary sinuses). Yet, an improved understanding of the microstructure and metabolic changes that accompany optic neuritis may offer a biomarker for MS.

Chemical exchange saturation transfer (CEST) is a new technique that exploits the exchange of protons between water and labile, mobile protons associated with proteins/peptides [3], and neurochemicals (glutamate) [4] by using a spectrally selective RF irradiation to saturate mobile protons and assess the signal attenuation on water, which is known to be sensitive to the exchange rate and concentrations of these labile proteins. Previous work using CEST MRI has indicated that amide protein (APT) content may be sensitive to protein/peptide changes in normal appearing white matter [5], as well as changes in pH [6]. In the ON, optic neuritis may cause an alteration of the cellular composition of the ON, which will then be reflected in the protein content, or in the acidity of the surrounding tissue. While CEST imaging has been used to assess brain [7] tissue microstructure, similar studies in the human ON have not been explored due to both the size of the nerve and the poor contrast between neurological and surrounding connective tissue. We therefore implemented a high-resolution, pulsed-saturation APT CEST protocol that utilizes an multi-shot EPI train combined with a ProSet fat suppression in order to characterize the APT CEST effect in healthy ON tissue to set the stage for further examinations of patients with history of optic neuritis.

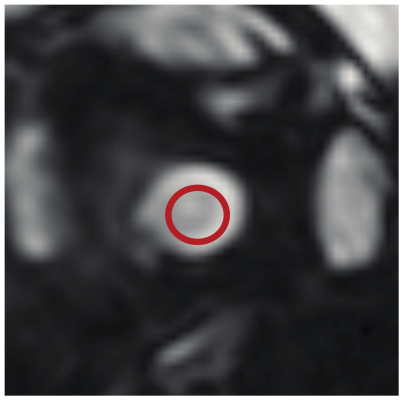

**Figure 1:** Example CEST image ($\Delta\omega = 3.54$ ppm) for ON. ROI represents area used for evaluation.

**Methods:** Nine healthy volunteers (mean age 27.9±5.3 years, 4 male) were imaged using a 3.0T Achieva whole body, multi-channel transmit MR scanner (Philips Healthcare, Best, The Netherlands). A quadrature body coil was used for excitation and an 8-channel head coil was used for signal reception. A 3D imaging volume sufficiently large to accommodate a 121 ProSet fat suppression pulse coronal to both ON was deployed. CEST data were acquired using a multishot 3D CEST-prepared EPI sequence [8]. For CEST preparation, a single-lobe sinc pulse with Gaussian apodization was applied with duration of 75 ms, maximum pulse amplitude of 2 μT, and offset frequencies ($\Delta\omega$) from -4.5 to 4.5 ppm, with an offset of 100,000 ppm for normalization at the beginning and the end of the acquisition, resulting in 37 CEST-weighted images. Additional imaging parameters included: TR = 154 ms, excitation flip angle = 20°, SENSE factor = 2, FOV = 100 x 152 x 36 mm$^3$, resolution = 1.0 x 1.0 x 2 mm$^3$, and a duration of 12.5 minutes. In order to minimize ON motion during the sequence, volunteers were asked to focus on a fixation cross for the duration of the CEST acquisition.

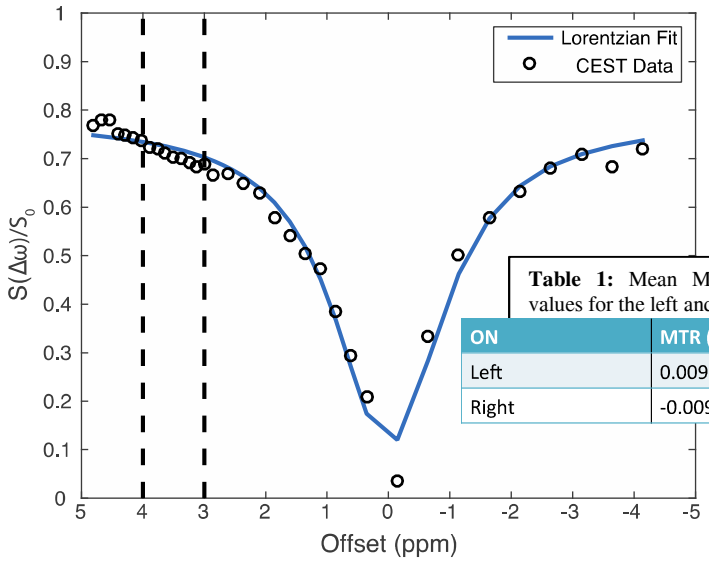


**Figure 2:** Sample CEST data and Lorentzian fit of the ROIs in the ON. Dashed lines represent the area used for AUC analysis.

Normalized (to the mean of the $\Delta\omega$ = 100,000 ppm data) signal intensities from ROIs placed within the left (L) and right (R) ON (Fig. 1) were fitted to a single Lorentzian model of the direct water saturation (DWS) curve [9], and shifted to account for B0 inhomogeneity. The integral of the residuals between the Lorentzian fit and the CEST data was calculated (AUC) between the 3 and 4 ppm. This spectral region was chosen because it has been shown that the APT effect is centered at 3.5 ppm downfield from water. A two-sample t-test was also performed in order to determine the asymmetry of the AUC measurements between the left and right ON.

**Table 1:** Mean MTR asymmetry and %AUC values for the left and right ON.

| ON | MTR (3.5 ppm) | %AUC (3-4 ppm) |
|---|---|---|
| Left | 0.009±0.05 | 1.74±1 |
| Right | -0.009±0.06 | 1.63±1 |

**Results & Discussion:** A representative CEST-weighted image near the amide resonance is shown in Fig.1. Note the change in contrast between the ON and surrounding CSF an d excellent fat saturation. A CEST z-spectrum (points) and resulting Lorentzian fit (line) is shown in Fig. 2. Importantly, the area between the dashed lines indicates the limits for the AUC analysis. The mean %AUC values and MTR asymmetry values are shown in Table 1. There was found to be no difference between each eye for both the MTR asymmetry ($p = 0.51$) and %AUC ($p = 0.79$). Note the slight signal deviation from the fit between 3 – 4 ppm indicating sensitivity to the CEST effect driven by the APT resonances.

These findings suggest that CEST can be accurately quantified in healthy ON at 3T. This is promising as optic neuritis is the presenting symptom in many cases of MS [1,2], and the amide protein content may be reflective of early protein change in normal appearing white matter and may provide an effective biomarker for MS prognosis. Further work includes acquiring longitudinal data to ensure this method is robust against temporal changes, as well as utilizing this method to measure these CEST-derived indices in patients with optic neuropathies.

**References:** [1] Balcer. N Engl J Med 2006(354):1273. [2] Shams. Int MS J. 2009(16):82. [3] Zhou. MRM. 2004(51):945. [4] Cai. Nature Medicine. 2012(18):302. [5] Dula. MRM. 2011(66):831. [6] Sun. MRM. 2011(65):588. [7] Jones. MRM. 2006(56):585. [8]. Sled. MRM 2001(46):923. [9] Jones. MRM. 2012(67):1579.

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