CEST MRI of Cortical Gray Matter in Multiple Sclerosis

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PURPOSE: It is increasingly being recognized that in MS, cognitive impairment is a major manifestation seen in all subtypes of MS that can hinder a patient's day-to-day function as much as, or even more significantly, than motor function, and is the root cause of many patients being unable to be gainfully employed. It is estimated that cognitive dysfunction affects 40- 70% of patients with MS, typically including memory, concentration and attention, speed of processing information and executive functioning.

METHODS: Thirteen healthy subjects and three MS patients were scanned on the Philips 7T Achieva scanner. Six of the healthy subjects underwent repeat scans approximately two months after the initial scan. The protocol included two CEST scans. The first CEST acquisition included full-brain coverage (33 slices) using a 3D gradient echo with multi-shot EPI (factor = 7) readout, a 1.5 × 1.5 × 2.5 mm^3 resolution, TR/TE/flip = 65ms/7.2ms/5°, and binomial fat saturation. Saturation parameters were optimized for observation of the amide proton transfer (APT) at frequency offset of 3.5 ppm downfield (Δω=3.5ppm) resulting in a B1 = 2 μT and 25-ms duration swept between Δω= -5.0ppm to 5.0ppm with a Δω step of 0.2ppm and 14 reference (no CEST saturation, S_0) scans. The acquisition time was 9:10 min. The second CEST protocol was a single-slice (5-mm) scan optimized for observation of protons associated with glutamate and/or glutamine (gluCEST)[1] where Δω=3.0ppm. Imaging used a 2D gradient echo with multi-shot TFE (40 shots) readout with in plane resolution of 1.9 × 1.9 mm^2 on a slice located slightly superior to the corpus callosum. The CEST saturation parameters were B1 = 4.25 μT and 10-ms duration x 100 pulses at a 90% duty cycle swept between Δω= -5.0ppm to 5.0ppm, Δω step = 0.2ppm, for a total acquisition time of 11:36 min.

The CEST spectrum for each voxel is normalized, corrected and fit to a single-Lorentzian[2] and the minimum spectral intensity is shifted to an offset Δω=0ppm for B0 correction. The CEST effect from both acquisitions was quantified using both the typical asymmetry measure and the integration of the residuals of the Lorentzian fit around the resonance of interest. From a high-resolution MPRAGE acquisition, the gray and white matter were segmented and applied to the calculated CEST-derived indices.

RESULTS: An example of APT CEST results are shown in **Fig. 1** in which the CEST effect due to APT was quantified via asymmetry (left) and the Lorentzian fit residual integration between Δω = 3.25 and 3.75 (right). Using the gray matter mask, for APT (3.5ppm) as well as resonances at 2.0ppm (hydroxyl protons) and 3.0ppm (amine protons) histogram results were generated and shown in **Fig. 2**. Note that the distributions at 2.0 ppm and 3.5 ppm show a downward shift in MS (green) relative to that of the healthy subjects (blue). gluCEST (Δω=3.0ppm) asymmetry maps are shown in **Fig. 3** demonstrating excellent contrast between white/gray matter with the gray matter having higher CEST effects at this resonance. The MS patient (right) shows elevated gluCEST effects on the left side but diminished effects in the right cortical gray matter compared to the healthy subjects. GM masks were applied to the whole cohort and histograms are shown in **Fig. 4** in which the mean gluCEST of all gray matter voxels in healthy subjects (blue) and MS patients (red) show a downward shift for the patient data with known cognitive impairment.

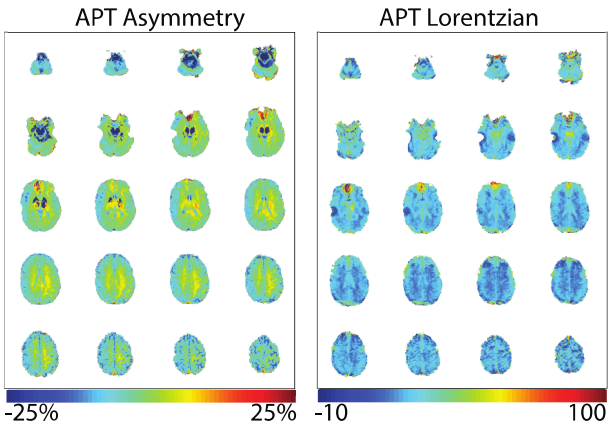

Figure 1 – CEST effects caused by amide proton transfer (APT) as calculated using asymmetry (left) and Lorentzian fitting (right) for an example healthy subject.

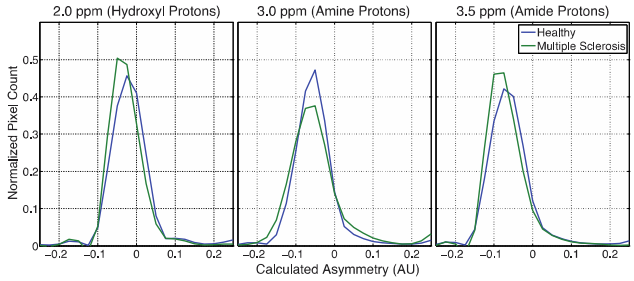

Figure 2 – Histogram analyses of segmented gray matter in all healthy (blue) and MS patients (green).

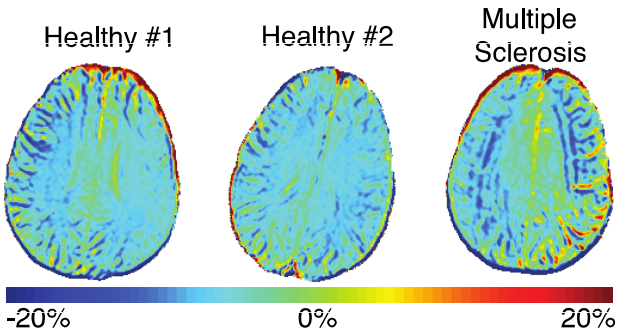

Figure 3 – Comparison of gluCEST asymmetry maps in two healthy subjects and one multiple sclerosis patient showing higher gluCEST effects in gray matter.

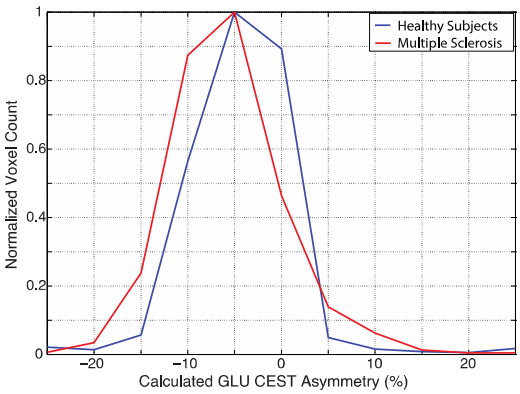

Figure 4 – Histograms of gluCEST with lower effects in MS gray matter.

DISCUSSION – Observation of calculated APT and gluCEST maps (Figs. 1 & 3) indication high data quality and sensitivity to gray/white matter while histogram analyses of MS patients with known cognitive impairment (Figs. 2 & 4) indicate initial sensitivity of the CEST methods to the pathology of cortical gray matter damage.

CONCLUSION – Using the signal enhancement of CEST MRI, we have established preliminary sensitivity to the pathological changes occurring in the gray matter in MS they could be driving clinically-observed cognitive challenges. Future work will include comparison of CEST metrics with neurocognitive measures.

REFERENCES: 1. Cai K, et al., Nat Med. 22;18(2):302-6. 2. Jones CK, et al., NeuroImage 77:114-124.