

# Magnetization transfer (MT) and endogenous Chemical exchange saturation transfer (CEST) effects in patients with clinically isolated syndrome

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**Introduction:** Multiple sclerosis (MS) is an autoimmune disease affecting the nervous system and causing various neurological complications mainly due to demyelination and axonal loss. Magnetization transfer (MT) is an important MRI measure in MS and the MT effect can be assessed qualitatively using magnetization transfer ratio (MTR) maps. Previous studies have shown that it is possible to produce high resolution MTR images at 7T within SAR limits. If the off-resonance frequency is altered then the MT effect can be used to construct a z-spectrum. A distinctive peak is observed in the z-spectrum of the human brain, at -1.05k Hz offset from the water frequency at 7T. This is caused by endogenous chemical exchange saturation transfer (CEST) between amide (chemical group attached to the peptide bond) and water protons [1,2]. Here we obtain MTR images for negative (MTR<sub>-</sub> sensitive to MT + CEST effects) and positive (MTR<sub>+</sub> sensitive to just MT effects) frequency offsets of the saturation and compare the distributions of these parameters in NAWM of healthy controls and patients with Clinically Isolated Syndrome (CIS: a condition that is likely to lead to MS).

**Methods:** Ten patients with CIS were recruited from Nottingham University Hospital. Six age-sex matched healthy volunteers were also recruited, and both groups were consented according to local ethics approval. Scanning was performed on a 7T Philips Achieva system, equipped with whole body gradients, a 16-channel receive coil and head only volume transmit coil. MT images were acquired using a 3D MT-TFE sequence (1x1x1.5mm resolution; TE=5.7 ms; TR=9.8 ms; 20 slices; total scan time =8:22min) [1] for no saturation and for pulsed saturation. The pulsed saturation applied as a train of 20 off-resonance pulses (13.5 μT Gaussian-windowed, sinc pulses with a bandwidth of 200 Hz and off-resonance by ±1.05 kHz (3.5ppm), with 50 ms between each pulse). Images were co-registered and MTR and Asymmetry (CEST) maps were calculated on voxel by voxel basis according to

$$MTR_{-} = (S_{MT0} - S_{MT-}) / S_{MT0} \quad MTR_{+} = (S_{MT+} - S_{MT+}) / S_{MT0} \quad CEST = MTR_{-} - MTR_{+}$$

(S<sub>MT+</sub> for offset +1.05k Hz, S<sub>MT-</sub> for offset -1.05k Hz and S<sub>0</sub> for no saturation). The scanning protocol included field map and a B1 map to correct the MT images for the effect of B1 inhomogeneity [3,4]. An MPRAGE image with grey matter approximately nulled was used in SPM5 to create a mask of the NAWM [5]. MTR images were then registered to the MPRAGE image, so that the NAWM of the MTR and CEST maps could be segmented. Normalized histograms of MTR values in NAWM were plotted. The mode (peak position), Full Width at Half Maximum (FWHM) and area under the curve for left and right tails of histograms (tails delineated from point where histogram reached half maximum) were calculated. In order to test the reproducibility of our measurements, one healthy subject was scanned on 5 occasions using the same scanning protocol described above.

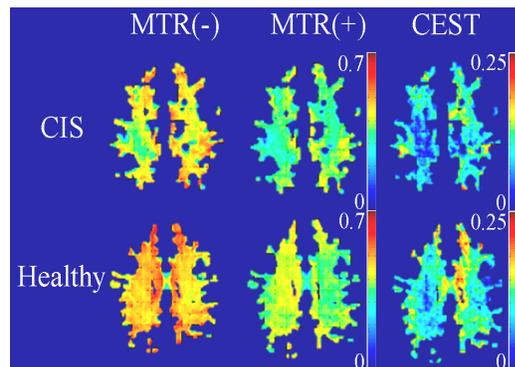
**Results:** Fig.1 shows representative MTR<sub>+</sub>, MTR<sub>-</sub> and CEST images from a CIS patient and healthy subject. Fig.2. shows the MTR<sub>-</sub> and MTR<sub>+</sub> histograms averaged over all CIS and healthy subjects. The individual data are summarised in table 1 and show significant differences between patient and controls in terms of peak position (mode) and skew of the histogram (from area under tail), but the data suggest that MTR<sub>-</sub> (which includes the CEST effect) provides greater discrimination between patients and controls. The MTR histograms were reproducible: the five repeats on one subject gave mode =0.44±0.02, height=0.16±0.001 and FWHM=0.10±0.004. Fig.3 correlates MTR<sub>-</sub> against MTR<sub>+</sub> for (A) a healthy subject (B) a CIS patient. Similar results were obtained in other subjects. Again it is clear that the NAWM of the control subject has larger values of MTR<sub>-</sub> than the patient. The centre of mass and distribution of the pixels in the corpus callosum is indicated by the grey cross and for the patient the centre of mass and distribution of the MTR values in the lesions is shown by black crosses.

| Table 1: Summary of histogram parameters averaged over all subjects in group. | MTR <sub>+</sub> (no CEST) |           |          | MTR <sub>-</sub> (CEST) |           |         |
|---|----------------------------|-----------|----------|-------------------------|-----------|---------|
|   | MS                         | Controls  | p-values | MS                      | Controls  | p-value |
|   | Mean±sd                    | Mean±sd   |          | Mean±sd                 | Mean±sd   |         |
| Mode (peak position)  | 0.37±0.03                  | 0.39±0.01 | 0.03     | 0.44±0.03               | 0.47±0.02 | 0.01    |
| FWHM  | 0.10±0.01                  | 0.08±0.01 | 0.01     | 0.10±0.02               | 0.09±0.01 | 0.05    |
| Area of low tail  | 0.16±0.04                  | 0.14±0.01 | (0.10)   | 0.20±0.06               | 0.15±0.02 | 0.05    |
| Area of high tail   | 0.13±0.01                  | 0.15±0.01 | 0.07     | 0.13±0.01               | 0.14±0.02 | 0.04    |

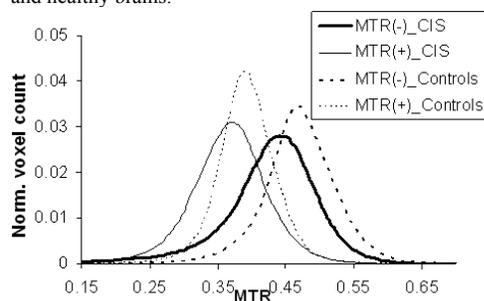
**Discussion:** The MTR<sub>-</sub> values are larger than MTR<sub>+</sub> values in the NAWM. This is clear in the maps (fig 1), histograms (fig 2) and slope of the fitted line in the MTR<sub>-</sub> versus MTR<sub>+</sub> plot (fig.3) and is assumed to be due to the CEST contribution to the MTR spectrum at ~-1.05k Hz [1]. The data also show that MTR values are reduced in CIS patients (figure 2 and table 1), although the effect is more pronounced if the data also include the CEST effect (i.e. MTR<sub>-</sub>). This may have implications for designing MT experiments. MT and CEST are not affected by the same physical processes but may both reflect myelination in the human brain. Plots of MTR<sub>+</sub> versus MTR<sub>-</sub> (fig. 3) provide a method of determining whether there are any pixels where MTR<sub>+</sub> and MTR<sub>-</sub> are uncoupled. The visible lesions clearly had very low MT values, and may show slightly larger changes on MTR<sub>-</sub> than MTR<sub>+</sub>.

**Conclusion:** The endogenous CEST effect may provide additional contrast in MS patients at 7T. This study was of CIS patients, and they will now be followed up to determine the effect of any disease progression to MS on the NAWM spectrum and the coupling of MTR<sub>+</sub> versus MTR<sub>-</sub> values.

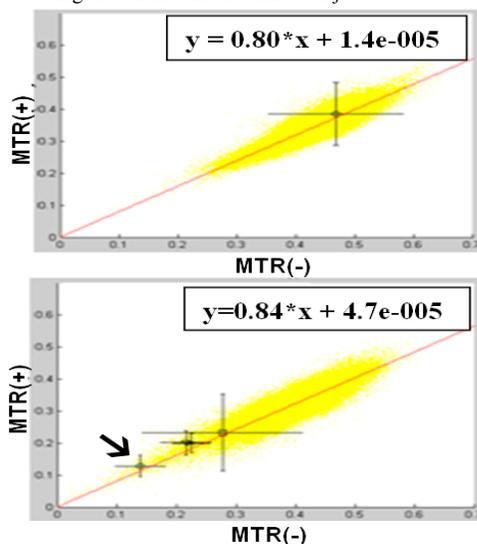
**References:** (1)Mougini et al, NeuroImage. 2010. 49: p 272-81 (2) Blakeley, J.O. et al, Neurology 2007. 68 : A288 (3) S. Ropele et al, MRM. 2005. 53 : p 134-140 (4) R. Samson et al. MRI. 2006. 24 : p 255-263 (5) <http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>. **Acknowledgements :** The Hashemite University, Jordan , for my studentship.



**Figure.1** MTR, MTR<sub>+</sub> and CEST images CIS patients and healthy brains.



**Figure 2:** Histograms of MTR values in NAWM averaged over all CIS or control subjects



**Figure 3:** MTR<sub>-</sub> – MTR<sub>+</sub> correlation