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# A 3-year follow-up study of enhancing and non-enhancing multiple sclerosis (MS) lesions in MS patients demonstrating clinically isolated syndrome (CIS) using a multi-compartment T2 relaxometry (MCT2) model

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## **Synopsis:**

Obtaining information on condition of tissue microstructures (such as myelin, intra/extra cellular cells, free water) can provide important insights into MS lesion. However, MRI voxels are heterogeneous in terms of tissue microstructure due to the limited imaging resolution owing to existing physical limitations of MRI scanners. Here we evaluated a multi-compartment T2 relaxometry model and then use it to study the evolution of enhancing (USPIO and gadolinium positive) and non-enhancing lesions in 6 MS patients with CIS characteristics over a period 3 years with 7 follow-up scans post baseline.

## **Introduction:**

Demyelination occurs at the onset of MS accompanied by macrophage intervention<sup>1,2</sup>. This is followed by axonal damage. Continuous tissue injuries cause inflammation in lesion affected regions of the brain. Advanced MRI techniques such as T2 multi-echo MRI sequences and diffusion imaging can help obtain brain tissue microstructure information.

Myelin, intra/extra-cellular fluids, and free water can be distinguished on the basis of their T2 relaxation times<sup>3</sup>. Myelin has a very short-T2<sup>3</sup> and its presence in WM is quantified by a variety of approaches<sup>3-7</sup>. The most popular approach is to obtain the water fraction (WF) corresponding to myelin (myelin water fraction (MWF)) in a tissue<sup>3-7</sup> from a multi-echo spin echo (SE) T2 MRI. However, since MWF is a relative measure, a decrease or increase in it only conveys a part of the information. In this work we use a multi-compartment T2 relaxometry (MCT2) model<sup>8</sup> to obtain WF corresponding to tissues with short-, medium- and high-T2 relaxation times. We perform test-retest experiments on 4 healthy controls (HC) to demonstrate the reproducibility of the WF estimates obtained from this model. A 3-year follow-up study is performed on 6 MS patients demonstrating clinically isolated syndrome (CIS). We study evolution of WFs in enhancing and non-enhancing MS lesions in white matter (WM).

## **Method and materials:**

### **MCT2 model:**

In the MCT2 model<sup>8</sup>, the T2 space is modeled as a weighted mixture of three continuous Gaussian probability density functions representing the three T2 relaxometry compartments with short, medium and high decaying components with respect to their T2 relaxation times. The short-T2 WF (WF<sub>S</sub>) provides information on myelin<sup>3</sup> and highly myelinated axons<sup>10</sup> in WM. The medium-T2 WF (WF<sub>M</sub>) correspond to the intra/extra-cellular matters<sup>3,10</sup>. The high-T2 WF (WF<sub>H</sub>) correspond to cerebrospinal fluids and inflammation in WM due to lesions.

### Reproducibility study:

Test-retest scans were performed for 4 HC. Average values in 8 WM ROIs were computed. A Bland-Altman plot was observed for assessing the reproducibility of the WF estimates. Similar to a previous study<sup>13</sup> we used this approach to obtain the reproducibility threshold value of WF estimates.

Data: 3T MRI scanner, first echo time (TE)=9ms, echo spacing ( $\Delta$ TE)=9ms repetition time (TR)=2030ms, number of echoes ( $n_{\text{echoes}}$ )=32, voxel dimensions ( $v_d$ )=1.64x1.64x4mm<sup>3</sup>. All images were registered<sup>11,12</sup> to a common T2-weighted image.

### MS lesion study:

Six MS patients demonstrating CIS condition were scanned at the baseline, and follow-up scans at month-{3,6,9,12,18,24,36}. The median age of patients included in this study was 28.5 years (at baseline) and there were equal number of male and female subjects. T2 relaxometry data: 3T MRI scanner, first TE=13.8ms,  $\Delta$ TE=13.8ms, TR=4530ms,  $n_{\text{echoes}}$ =7,  $v_d$ =1.3x1.3x3mm<sup>3</sup>, acquisition time=7minutes. For months-{0,3,6,9}: transverse SE T1-weighted images (1x1x3mm<sup>3</sup>) were acquired before and after USPIO infusion (SHU-555C;40 $\mu$ mol Fe/kg body weight over 30minutes) for obtaining USPIO enhanced lesions. A scan was done 24 hours later to obtain post-USPIO enhancement images. Transverse SE T1-weighted images (1x1x3mm<sup>3</sup>) post gadolinium contrast agent infusion (0.1mmol/kg gadopentetate dimeglumine) were acquired to find gadolinium enhanced lesions.

Following lesion types<sup>14</sup> were studied:

- (U+): Appear on post-contrast USPIO and Gadolinium scans.
- (Gd+): Appears on post-contrast Gadolinium scan, but not in (U+).
- (L-): MS lesion ROI not in (Gd+) and (U+).
- (E+): These are enhancing lesions and appear on (Gd+) or (U+)

All images are registered to 3D-FLAIR image (1x1x1mm<sup>3</sup>) acquired at the baseline. We analyzed 111(L-), 23(Gd+) and 6(U+) lesions.

We studied percentage of lesions in each type that underwent changes above the reproducibility threshold between an acquisition and its follow-up, and the evolution of MCT2 WF estimated over a period of 36 months.

The protocols were approved by the institutional review board of Rennes University Hospital, and all participants gave their written consent.

### Results and discussion:

Figure-1 shows WF maps of a healthy control.

The reproducibility results (refer Figure-2) show that the 95% limits of agreement (LoA) for both  $WF_s$  and  $WF_m$  are 0.013.

The percentage of lesions (PoL) undergoing change in  $WF_s$  above LoA (refer Figure-3(a)) are relatively smaller for (L-) than (E+) lesions. The percentage of lesions undergoing change in  $WF_s$  (refer Figure-3(a) and 3(c)) above LoA reduce after 6 months. In general, (L-) have lesser PoL undergoing change above AoL as compared to (Gd+) and (U+).

The evolution of WFs in each lesion type is shown in Figure-4.

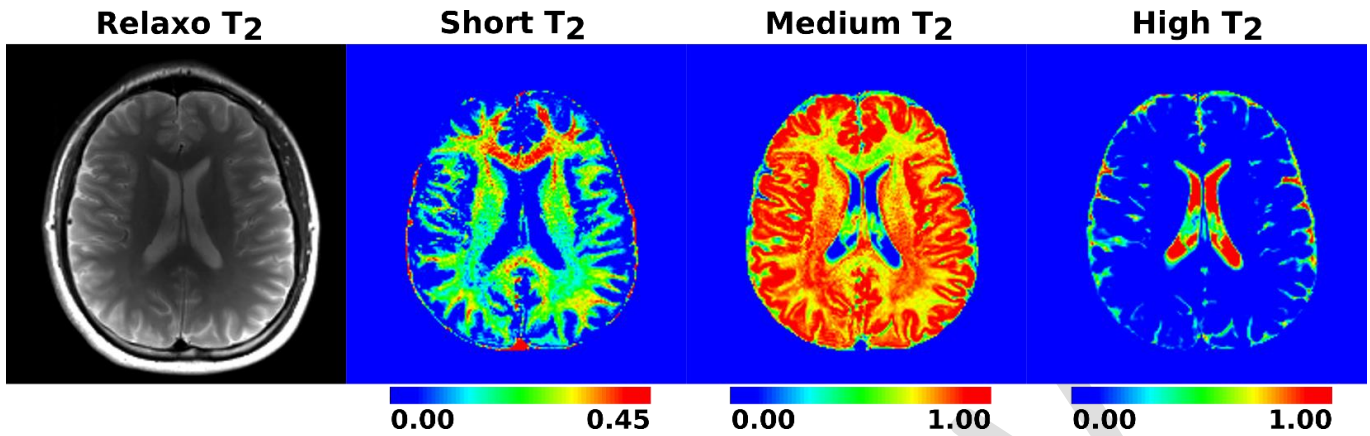


Figure 1: Water fractions estimated for a healthy volunteer. Water fraction maps estimated appear normal for a healthy subject, such as the genu has higher short-T2 water fraction values than the frontal white matter.

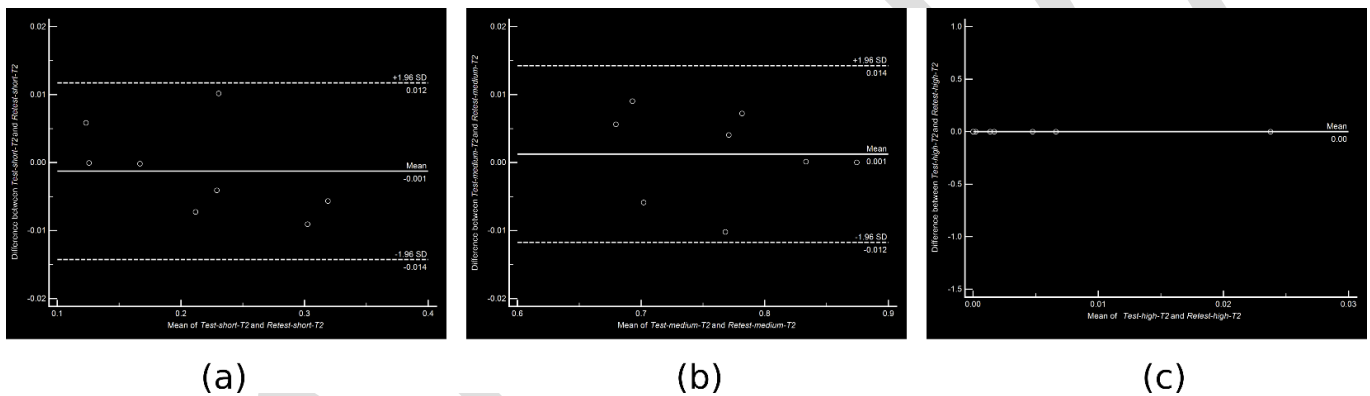


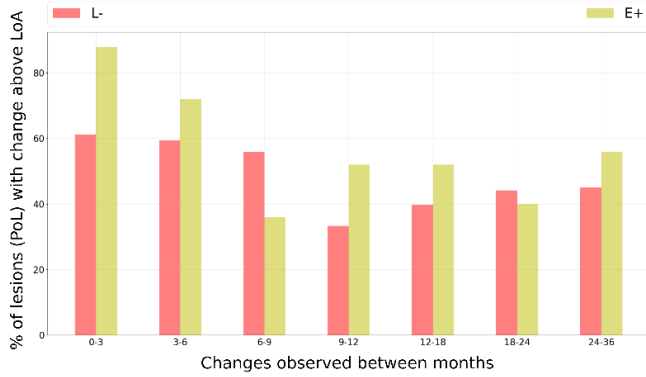
Figure 2: Bland-Altman plots for test-retest experiments for (a) short-T2, (b) medium-T2 and (c) high-T2 water fraction estimations for 8 white matter ROIs in 4 healthy controls. Results shows a high agreement between the test-retest experiments with limits of agreement (LoA) being 0.013 for short-T2 and medium-T2 WF test-retest estimations. The high-T2 water fraction estimation are in perfect agreement.

### Conclusion:

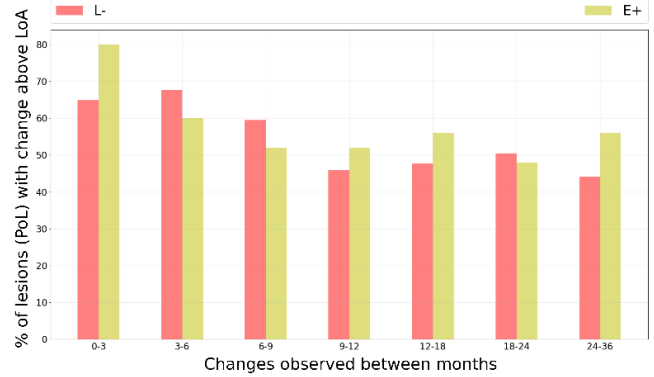
(U+) lesions showed higher variation in initial months as compared to (Gd+) and (L-). The MCT2<sup>8</sup> estimates are reproducible and provided insights into the lesion that corroborate with pathological studies<sup>2</sup> of MS lesions. In future we intend to perform more rigorous statistical analysis to evaluate if the MCT2 estimates can significantly differentiate among lesion groups studied in this abstract.

### Acknowledgements:

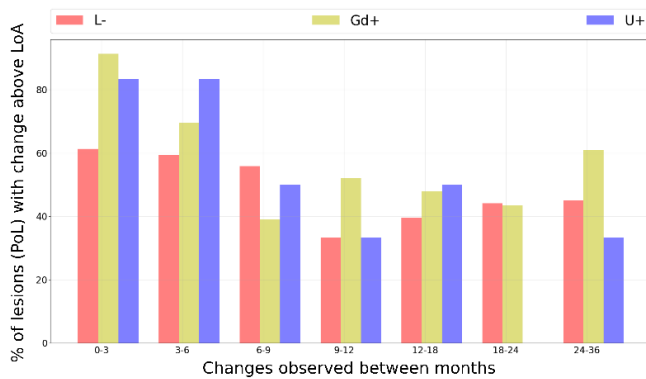
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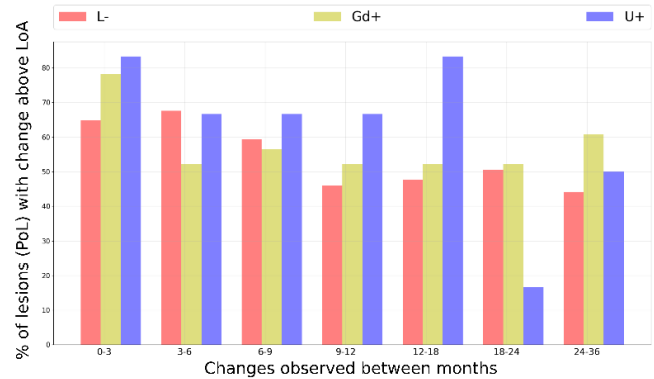
(a)



(b)

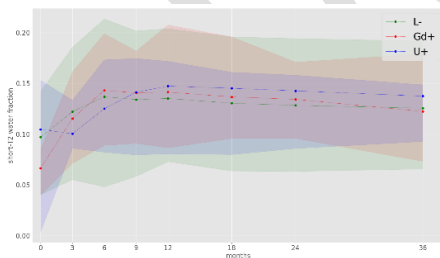


(c)

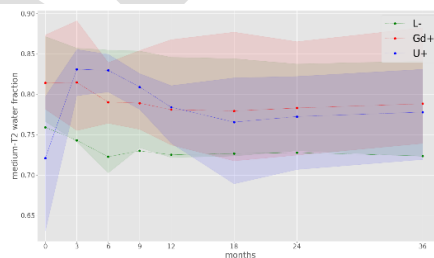


(d)

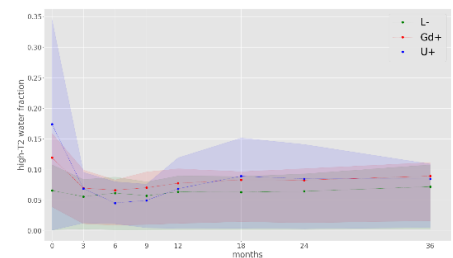
Figure 3: Percentage of Lesions (PoL) undergoing change in water fraction (WF) more than the limit of agreement (LoA) found from the Bland-Altman plots in Figure-2 are shown here. The x-axis shows the duration (in months) between which the changes were computed. Comparison in PoL change above LoA for (a) Short-T2 WF and (b) medium-T2 WF for (L-) and (E+) lesions. Comparison in PoL change above LoA for (c) Short-T2 WF and (d) medium-T2 WF for (L-), (U+) and (Gd+) lesions. Higher PoL in (E+) having  $WF_M$  above LoA might be an indication of increased extra-cellular matter (as macrophage) interventions in early lesions.



(a)



(b)



(c)

Figure 4: Evolution of (a) short-T2 ( $WF_S$ ), (b) medium-T2 ( $WF_M$ ) and (c) high-T2 ( $WF_H$ ) water fraction in (L-), (Gd+) and (U+) lesion over a period of 36 months. The  $WF_S$  values of (U+) lesions increase after month-6 compared to (Gd+) and (L-) lesions, indicating a delayed remyelination. This might be explained as (U+) lesions are in an earlier stage compared to (Gd+) and (L-) and hence have a delayed recovery. The high  $WF_M$  values in (U+) might be attributed to the known increased extra-cellular matter presence in early lesions. By the end of month-36, (L-), (U+) and (Gd+) attain similar  $WF_S$  and  $WF_H$  values.

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