Multi-parameter mapping of *post-mortem* lumbar spinal cord tissue in multiple sclerosis

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Target audience: Scientists and clinicians interested in spinal cord Magnetisation Transfer (MT) imaging methods.
Purpose: To compare different semi-quantitative Magnetisation Transfer imaging approaches in *post-mortem* spinal cord.
Introduction: The spinal cord (SC) is affected in neurological disorders such as multiple sclerosis (MS). Several studies have investigated Magnetisation Transfer Ratio (MTR) changes in the SC in MS and found significant reductions[1,2], thought to be due to demyelination and axonal damage. However, the MTR is influenced by T_1 relaxation and B_1 inhomogeneities as well as MT exchange, and is thought of as being only 'semi-quantitative', since it is dependent on sequence acquisition parameters. Recently, a more quantitative parameter sensitive to myelin, MT_{sat}, has been proposed[3], which enables the separation of the T_1 relaxation contribution, and is inherently independent of B_1 inhomogeneities[3,5]. We investigated the feasibility of performing tissue-specific multi-parametric measurements in 1 healthy and 1 MS *post-mortem* cord samples, and compared the contrast achievable between normal-appearing white matter (WM), grey matter (GM), and a cord lesion for MTR and MT_{sat}. **Methods:** Healthy and MS lumbar SC samples (sex: female, age at decease: 67 years, MS subtype: chronic, last assessed EDSS: 7) were diffusion fixed in formalin solution after death and scanned in paraformaldehyde solution using a 3T Philips Achieva system (Philips Healthcare, Best, The Netherlands) with a 32-channel coil. A 3D slab-selective multi-echo Fast Field Echo sequence (voxel size=0.25x0.25x2mm^3, 6 gradient echoes, TE/ΔTE=4.3/4.7ms) was performed 3 times, resulting in T_1 (T1w) (TR=49.8ms, flip angle (α)=23°), proton density (PDw) (TR=49.8ms, α =9°), and MT weighting (MTw) (12ms Sinc-Gaussian off-resonance MT pulse of flip angle=360°, offset frequency=1kHz, TR=51.4ms, α =9°). The spatial distribution of the B_1 transmit field was measured using a 3D actual flip angle imaging method[4] (α=60°, TR_1/TR_2=40/90ms, TE=7.5ms), to enable inhomogeneities correction of the T_1 maps. T_1, apparent PD (PD_{app}), T_2^* and MT_{sat} parametric maps were calculated according to[3,5], after averaging over all echoes, and an MTR map was calculated using the averaged PDw and MTw images. Regions of interest (ROIs) were manually drawn on the central 10 slices of the PDw volume in WM and GM (for the healthy sample) and normal-appearing WM (NAWM) and GM (NAGM), and a WM lesion (L) (for the MS sample). Percentage tissue contrasts compared to WM (or NAWM) were also computed for MTR and MT_{sat}. Paired t-tests were performed to test for differences in mean parameter values between tissue types. **Results:** Figure 1 shows single slice examples of manually drawn ROIs on the PDw images and parametric maps for the healthy and MS samples. Table 1 gives mean parameter values (± standard deviations (SDs)) within each tissue type ROI, with significant differences compared to (NA)WM indicated. GM/WM, NAGM/NAWM, L/NAWM and L/NAGM contrasts are greatly enhanced for MT_{sat} compared to MTR: 16.6%, 29.6%, 48.8% and 27.1% respectively for MT_{sat}, and 1.6%, 9.7%, 25.4%, and 17.4% for MTR.

	PDapp[10^6 a.u.]	**T_1**[ms]	**T_2***[ms]	**MTsat**[p.u.]	**MTR**[p.u]
WM	1.01(0.07)	413.0(45)	33.2(6)	6.1(1.0)	26.8(2.9)
GM	1.23(0.11)**	494.4(73)**	41.7(11)**	5.1(1.0)**	26.3(2.6)**
NAWM	1.14(0.10)	420.3(48)	35.0(7)	6.0(1.3)	26.6(2.8)
NAGM	1.44(0.09)**	530.5(54)**	50.0(11)**	4.2(0.8)**	24.0(3.0)*
L	1.61(0.19)**	601.0(118)*	61.4(18)**	3.1(1.0)**	19.8(4.4)**

Table 1*: Parameters mean values (±SD) in (NA)WM, GM and L ROIs. (*) and (**) indicate significant differences compared to WM or NAWM, with p<0.05 and p<0.01 respectively.*

Discussion and Conclusions: Multi-parameter mapping has been performed for the first time in *post-mortem* healthy and MS SC samples, and the potential for MT_{sat} to improve the differentiation of specific SC tissue types compared to MTR has been confirmed quantitatively. MT_{sat} is of particular interest since, unlike the MTR[5], it is minimally affected by T_1 relaxation and is less sensitive to B_1 inhomogeneities. Further sequence optimisation is required to reduce acquisition time whilst retaining sensitivity to differences in parameter values between tissue types. Assessment of the accuracy of parameter estimates is challenging since tissue relaxation properties are significantly altered *post-mortem* and following fixation. As expected, measured T_1 and T_2 were found to be considerably lower than *in vivo* cervical cord values[6]. T_2^* was also empirically validated by comparison with estimates obtained from a more dense dataset (12 echo times). MT_{sat} is higher than previously measured in the brain and SC *in vivo*[3,7], which may have been caused by several factors, such as the longer TR or relatively low offset frequency used in this study[4]. Additionally, our samples are from the lumbar cord level rather than the more commonly studied cervical levels, making it difficult to compare our results with previous measurements. Future work will include correlations with histological measurements in order to clarify the specificity of some of these observations and aid the translation to the clinical setting.

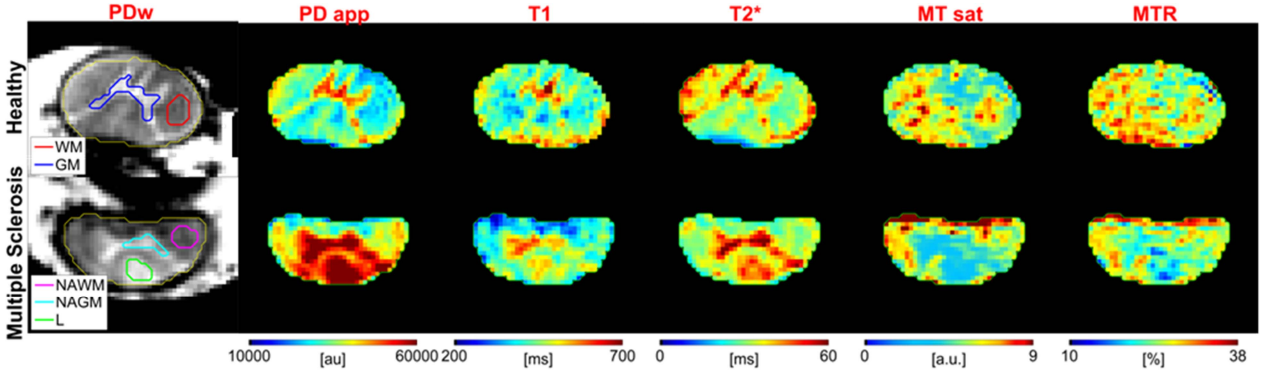

Figure 1*: Central slice PDw images with example ROIs in GM (**blue**), lateral column WM (**red**), NAWM (**purple**), NAGM (**light blue**) and lesion (**green**), PD_{app}, T_1, T_2*, MT_{sat} and MTR maps for healthy (**top**) and MS (**bottom**) cord samples.*

References: [1] Rovaris M *et al* Brain (2001);124:2540-9. [2] Filippi M *et al* Neurology (2000);54:207-13. [3] Helms G *et al* MRM (2008);60:1396-407. [4] Yarnykh V *et al* MRM (2007);57(1):192-200. [5] Helms G *et al* MRM (2010);64:1856. [6] Smith S *et al* MRM (2008);60:213–9. [7] Samson RS *et al* NMR Biomed (2013);26:1823-30. **Acknowledgements:** We thank the MS Society of the UK for funding. This work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme.