Multi-modal post mortem MRI at 7T to detect and quantify multiple sclerosis cortical grey matter pathology

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Introduction: Multiple sclerosis (MS) is a demyelinating and degenerative disease of the central nervous system (CNS) white matter (WM) and grey matter (GM). However, using standard MRI techniques focal pathological changes can only be detected easily in the WM. High resolution MR imaging using high field MRI systems promises better detection and quantification of MS GM pathology, thus enabling a more comprehensive depiction of MS pathology *in vivo*. Cortical GM pathology in MS can be divided into demyelinated GM lesions (GML) and non-lesional GM (NLGM) with no apparent demyelination [1]. To further explore the pathophysiology of MS *in vivo* it is important to be able to separate (i) GML from NLGM and (ii) both GML and NLGM from the white matter (WM) and cerebro-spinal fluid (CSF) compartments. Recent studies investigating GML *in vivo* have used either (i) double inversion recovery (DIR) and phase sensitive inversion recovery (PSIR) at 3T [2-4] or (ii) T_2*weighted (T_2*w) MRI as 7T [5].

Aim: In this study we aim to optimize multimodal 3D MRI acquired at 7T for (i) cortical GML detection and (ii) quantitative assessment of GML and NLGM. Isotropic voxel size is chosen to enhance lesion detection, delineation and volume assessment of the lesions, and for registration between the modalities.

Method: A formalin fixed hemisphere of *post mortem* brain from a 47-year-old female with MS was used. Time between death and tissue fixation was 39 hours. For scanning the brain hemisphere was taken out of its 10% formalin bath placed in a purpose-designed holder, and immersed in perfluorpolyether (to avoid susceptibility artefacts at the tissue air interface). MRI was performed on an Achieva 7T MRI scanner (Philips Medical Systems) equipped with a whole body gradient coil, a head only quadrature transmit RF coil and a NOVA 32 channel receiver coil. Sequences acquired were as follows: (i) T_2*w volume acquired at 300µm isotropic resolution using a 3D-TFE (TE/TR=15/46ms, FA=15° (6h)) onto which all the other sequences were registered; (ii) T_2-weighted (T_2w) MRI at 350µm isotropic resolution acquired with a 3D-TSE (TE/TR=90/3500 (12h11min)), (iii) PSIR acquired at 350µm isotropic with a 3D-TFE (TE/TR=9/3500ms, TI of 210ms (3h)), (iv) magnetization transfer ratio (MTR) maps at 350µm isotropic resolution acquired with a 3D-MT-TFE sequence (saturation via n= 20 off-resonance pulses with amplitude B1sat of 3.79µT, T= 50ms, bandwidth of 250Hz, applied at 1 kHz off resonance chosen to be sensitive to CEST effects observed in the spectra at 3.5 ppm) with TE/TR=10/21ms, FA=8° (5h45min), (v) double inversion recovery (DIR) at 350µm isotropic resolution acquired using 3D-TSE (TE/TR=144/10000ms, TI1/TI2=1850/260ms (5h)). Quantitative T_1, T_2 and T_2* maps were also acquired (at coarser resolution). All images were registered to the T_2* volume using fsl (http://www.fmrib.ox.ac.uk/fsl/) and volumes of interest (VOI) were manually drawn on each slice of the different volumes. Two independent researchers reviewed the different modalities and classified the lesions as: 1: purely cortical, 2: mixed, 3: subpial [1]. VOIs of five mixed and five purely cortical lesions, as well as adjacent NLGM were analysed on each modality independently, and results are summarized in figure 2.

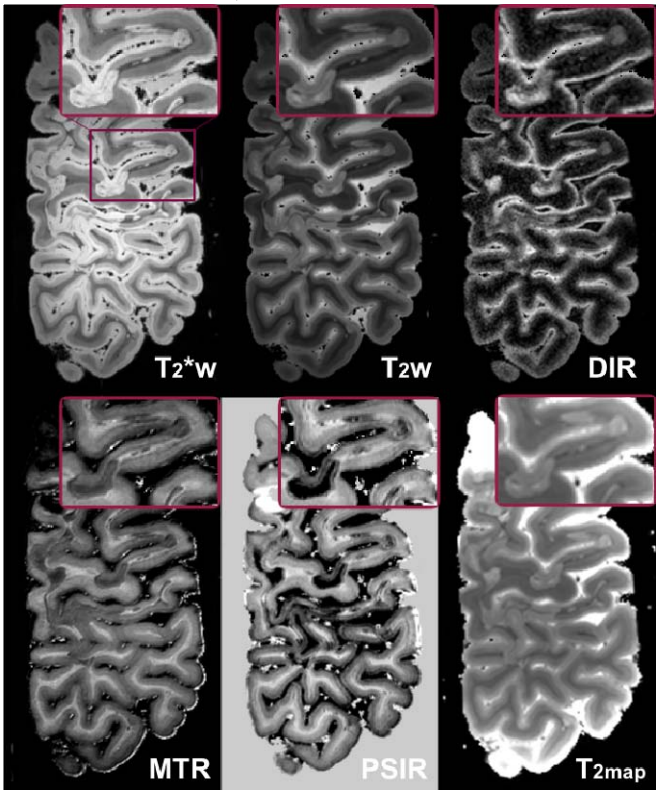

Figure 1: T_2*w, T_2w, DIR, MTR, PSIR images and T_2map, with insert on LGM tissue, all registered on the T_2* volume. Intra, mixed and juxta-cortical lesions are visible on all modalities.

Results: A similar amount of lesions were classified as mixed (N=137) as purely cortical (N=111), with no sub-pial lesion being detectable with confidence. Imaging parameters were successfully optimized for fixed post mortem MS brain (figure 1) and Contrast to Noise Ratio (CNR) was highest in the T_2w images followed by T_2*w for the different lesion types.

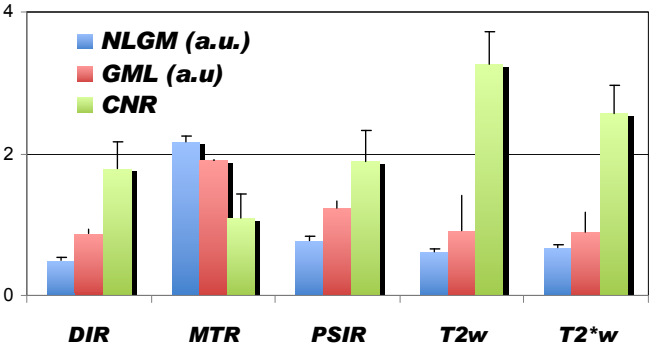

Figure 2: Signal (a.u.) for 10 VOIs in the GML and adjacent NLGM, together with corresponding CNR obtained on the different modalities.

Conclusion: This study has shown that T_2w MRI is the best technique to detect cortical GML in fixed *post mortem* MS brain, confirming earlier work[6] obtained using a small bore 9.4T system, and showing best the change in structure (myelin loss) occurring in GML. *Post mortem* brain MRI at 7T will allow comparison of the MR characteristics of pathological changes in GM due to MS, and will allow the MR properties of these lesions to be fully investigated. Our inability to detect sub-pial lesions may be due to (i) the limited sample size (N=1 brain hemisphere) (ii) the lack of non-MS-brain for comparison or (iii) the need for pathological confirmation of the MRI findings. We will therefore increase our sample size, include control brain in our study, and explore pathological correlates of the MRI techniques used.

Bibliography: [1]: Bo, L. *et al*, J Neuropathol Exp Neurol 62: 723-32, 2003. [2]: Geurts, JJ. *et al,* Radiology 236 (1): 254-260, 2005. [3]: Nelson, F. *et al*, AJNR 28 (9): 1645-9, 2007. [4]: Tallantyre, EC. *et al,* JMRI 32 (4) 971-7, 2010. [5]: Mainero, C. *et al*, Neurology 73 (13): 941-8, 2009. [6]: Schmierer, K. *et al,* Brain 133(3): 858-67, 2010.