Mapping the g-ratio within MS lesions

Mara Cercignani[1], Giovanni Giulietti[2], Barbara Spano'[2], and Marco Bozzali[2]
[1]*CISC, Brighton and Sussex Medical School, Brighton, East Sussex, United Kingdom,* [2]*Neuroimaging Laboratory, Santa Lucia Foundation, Rome, Italy*

TARGET AUDIENCE: Clinical and basic scientists with an interest in imaging biomarkers of multiple sclerosis.

PURPOSE: Quantitative MRI techniques, such as diffusion MRI (dMRI) and magnetization transfer (MT), are sensitive to changes induced by multiple sclerosis (MS), although they are likely to reflect different factors. While quantitative MT provides indices of myelination, validated in animal models and post-mortem studies [1], dMRI can infer the distribution of axonal radius and fiber density within an image voxel [2]. Against this background, Stikov et al [3] proposed a method based on MT and dMRI to measure the g-ratio, i.e. the ratio of the inner to the outer diameter of a myelinated axon. The g-ratio is a reliable index of axonal myelination, and can be related to the physiology and function of an axon. Its value is optimised to ensure the fastest possible axonal conductivity [4], with such an optimal value calculated to be around 0.7 in the CNS. Demyelination, remyelination and axonal degeneration are expected to affect the g-ratio, partially explaining the observed impairment in MS. Whole-brain g-ratio mapping in vivo has thus the potential to be a sensitive marker of pathology in myelinated axons, and to yield clinically useful information. Aim of this on-going study is to measure in-vivo the g-ratio inside MS lesions and to characterise its distribution in relationship to clinical symptoms.

METHODS: For this proof-of-concept paper we have included data from 2 patients, one with relapsing-remitting (RR) and one with secondary-progressive (SP) MS. Both patients received an MRI scan at 3T. Together with conventional FLAIR and dual-echo scans, we collected multi-shell diffusion-weighted data (10 b=0 volume, 30 diffusion directions with b=710 smm^{-2}, and 60 diffusion directions with b=2800 smm^{-2}), optimised for neurite orientation dispersion and density imaging (NODDI, [5]), and a quantitative MT scan based on a 3D gradient echo sequence, which collects a series of MT-weighted volumes with differing degrees of MT-weightings, a T1-mapping sequence, and a B1-mapping sequence. Lesions were outlined on the FLAIR scan using a semi-automated local thresholding contouring software (Jim 4.0, Xinapse System, Leicester, UK, http://www.xinapse.com/), and total lesion volume was computed for both patients. Quantitative MT data were analysed using in-house software, yielding a voxel-wise estimation of the relative size of the macromolecular proton pool, F. This index is considered a proxy of myelination, and it was recently shown to be directly proportional to the myelin volume fraction (MVF) [6]. Diffusion-weighted data were corrected for distortions and involuntary motion by affine registration, and analysed using the NODDI Matlab toolbox (http://mig.cs.ucl.ac.uk/index.php?n=Tutorial.NODDImatlab) to estimate voxel-wise the volume of the intra-cellular water compartment (V_{ic}) and of the isotropic component (V_{iso}). Quantitative MT and NODDI data were non-linearly co-registered using ANTs 1.9.x to bring all maps in the same space, and estimates of MVF and the fiber volume fraction (FVF) were derived as in [7]. A whole-brain map of the g-ratio can then be derived combining MVF and FVF as g-ratio = sqrt{ 1/ (1+MVF / FVF)}. T2 hyperintense lesion masks were transposed onto the g-ratio maps to extract the mean lesion g-ratio value, and also to automatically classify lesions based on their g-ratio value.

RESULTS: The patients' lesion loads were, respectively, 15.4 mL for the RRMS and 40.5 mL for the SPMS patient. Fig 1 shows the lesion discretised (using 0.1-wide bins) g-ratio maps, clearly indicating that the values within lesions are highly variable, ranging from 0.4 to 0.8 (normal-appearing white matter value: ~0.6-0.7). We classified every voxel within the lesion mask according to their g-ratio values (using bins of 0.1) and mapped the corresponding FVF and MVF in the 2 patients separately (Fig 2). While in the RRMS patient, a clear trend can be spotted, with MVF values decreasing faster than FVF values with increasing g-ratio, a more complex pattern emerges for the SPMS patient.

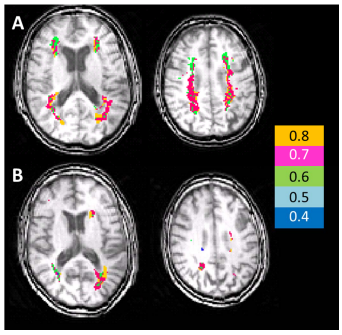

Fig 1. Discretized lesion g-ratio maps for the SPMS patient (A) and the RRMS patient (B).

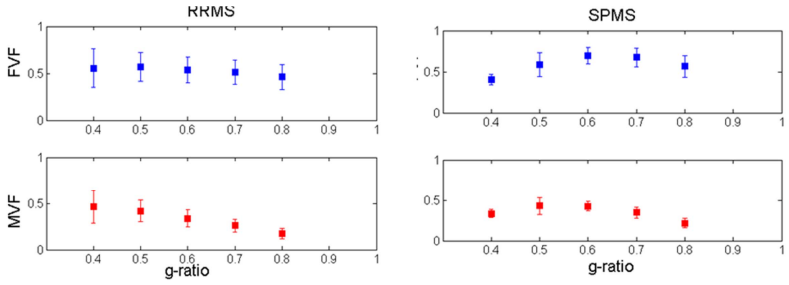

Fig 2. Average (+/- SD) FVF and MVF values within lesions as a function of the g-ratio, for the RRMS patient (left) and SPMS patient (right).

DISCUSSION. This proof-of-concept study confirms that g-ratio mapping is feasible in patients with MS. The variability of this parameter within white matter lesions fits with the heterogeneous pathological substrate likely to occur in this tissue. The MVF/FVF analysis suggests that in RRMS, demyelination/remyelination are the main events affecting the g-ratio, while a more complex interaction between axonal damage, gliosis and demylination is likely to occur within lesions of SPMS patients.

References: 1) Ou X, et al., Magn Reson Med. 2009 Feb;61(2):364-71. 2) Alexander DC. Magn Reson Med. 2008 Aug;60(2):439-48. 3) Stikov N, et al. Neuroimage. 2011 Jan 15;54(2):1112-21. 4) Chomiak T, Hu B. PlosOne 2009 Nov; 4(11):e7754. 5) Zhang H, et al. Neuroimage. 2012 Jul 16;61(4):1000-16. 6) Dula AN, et al. Magn Reson Med. 2010 Apr;63(4):902-9. 7) Campbell JSW, et al. Proc Joint annual meeting ISMRM-ESMRMB 2014: p393.