

Towards an in-vivo and post-mortem characterization of chronic multiple sclerosis lesions using susceptibility related mechanisms of contrast at ultra-high field MRI with R_2^* and phase images

B. Yao¹, F. Bagnato², E. Matsuura², H. Merkle¹, P. van Gelderen¹, H. McFarland², and J. H. Duyn¹

¹AMRI, NINDS, National Institutes of Health, Bethesda, MD, United States, ²Neuroimmunology Branch, NINDS, National Institutes of Health

Introduction: R_2^* and phase images derived from high-resolution 7 Tesla magnetic susceptibility-weighted MRI provide a rich contrast in healthy and diseased human brain. Yet, the sources that contribute to this contrast are not fully understood. Previous studies suggest that iron and myelin brain content may each contribute to R_2^* and phase in a different manner [1]. In this study, we used multiple sclerosis (MS) as a model of disease to investigate contribution of the iron and myelin content to pathological contrast. The pathological hallmark of MS is the classical demyelinated plaque. Iron was also shown to accumulate in chronic lesions as well as in peri-lesional areas [2, 3]. The imbalance of the iron/myelin ratio that can be present at variable extent in MS lesions and therefore could provide valuable clues to the role of iron and myelin in GRE contrast.

Methods: In-vivo study Twenty patients with MS (F/M = 11/9, age = 44 ± 10 y/o, EDSS score = 1.0-6.0) participated in this study. A 2D multi-echo Gradient Echo (ME-GRE) acquisition was performed with following parameters: TE = 15.5/ 30.0/ 44.5 ms, TR = 2 s, resolution = 0.31×0.31 mm², thickness/gap = 0.8/0.2 mm, flip angle = 75°, bandwidth = ± 31.25 kHz. 30 axial slices per slab and totally 1 to 3 slabs (varies among patients) were acquired to cover the all the lesion areas. A SENSE acceleration rate of 2 was used to shorten the scanning time. Quantitative R_2^* maps were obtained by using mono-exponential fitting. To remove phase wraps, the complex data were first smoothed by a Gaussian filter (FWHM = 30 voxels) to determine the macroscopic background phase. Continuous phase maps were then generated after subtraction of the phase background from the original data.

Post-mortem study Formalin-fixed brain specimens from a 70 y/o man who had died of pneumonia linked to secondary progressive MS were scanned using a 3D ME-GRE sequence. The tissue slices were first scanned on a GE 7T scanner, after which selected lesion areas were cut into $2 \times 2 \times 1$ cm³ pieces and imaged at 11.7T Bruker scanner with 0.1 mm isotropic resolution and TE = 3.9/ 10.4/ 16.9/ 23.4 ms. The R_2^* and phase maps were calculated using the same methods as above. Histochemical stains including Luxol Fast Blue stain for myelin, Perls' stain for iron and rabbit antibody stain for ferritin were performed and the results were compared with the MRIs.

Results: In-vivo The appearance of MS lesions in magnitude, phase and R_2^* was rather heterogeneous, with both positive and negative shifts occurring in phase and R_2^* . Some lesions (ring-type) lesions showed a distinct contrast at their perimeter. **Fig. 1** shows sample lesions from two cases. Patient 1 has lesions (solid arrow) with nodular shape in magnitude, phase and R_2^* images, while another lesion (dotted arrow) showed only prominently in magnitude and R_2^* . Patient 2 shows a ring type (solid arrow) or a semi-ring type (dotted arrow) lesion with uniform intensity distribution in magnitude and R_2^* but a prominent hypointense line at its perimeter in the phase image. **Post-mortem Fig. 2** shows an example of a MS plaque (indicated as L) in the white matter (W) between cortical gyri (C). The lesion is similar to the ring type lesion observed *in-vivo*. Both phase and R_2^* were hyperintense in a large part of the lesion perimeter. Histology showed increased iron and ferritin at this location, and a varying amount of myelin. Within the lesion, an area of high ferritin, iron, and myelin was found. This area (green arrow) showed increased R_2^* image but normal phase.

Discussion: The heterogeneity in MRI appearance correlated with varying content of myelin and iron, likely representing a varying nature or severity of the underlying pathological process. The results of the *post-mortem* study suggest a relationship between MRI parameters and iron content. The findings are consistent with the notion that both iron and myelin increase R_2^* , while they may have counter-acting effects on phase. This may be explained by a diamagnetic shift from myelin lipids off-setting the paramagnetic shift from iron.

References: [1] Duyn JH et al, *Proc Natl Acad Sci USA* 104: 11796-801, 2007; [2] Craelius W et al, *Arch Pathol Lab Med* 106:397-9, 1982; [3] Hammond KE et al, *Ann Neurol* 64:707-13, 2008

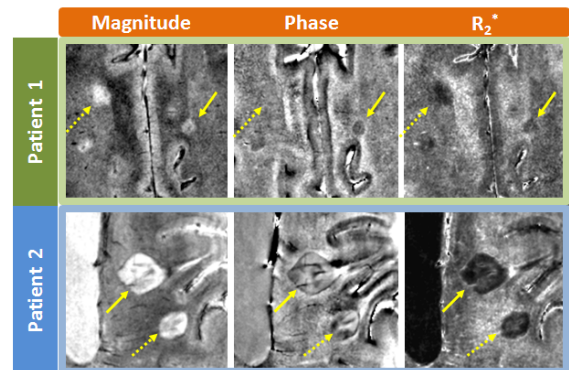


Fig. 1: In-vivo results

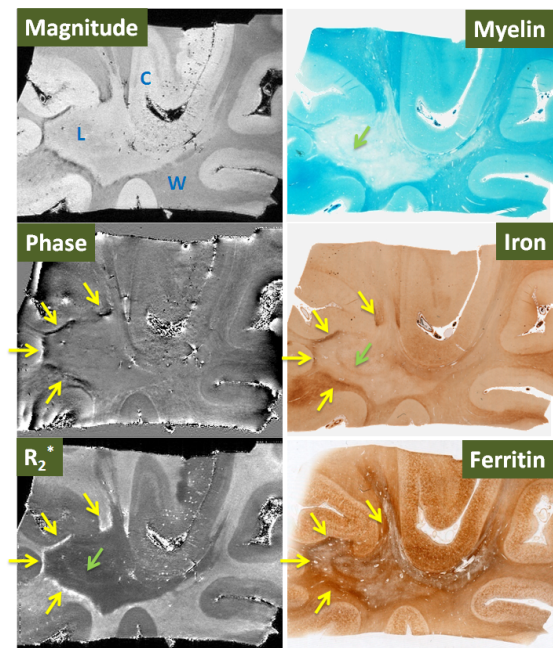


Fig. 2: Post-mortem results