Relationship between MR phase and tissue microstructure

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Introduction: Multiple Sclerosis (MS) is a demyelinating disease of the central nervous system. MS lesions in the human brain can be identified in MR phase images as regions with increased MR resonance frequency with respect to their surroundings. The source of this contrast has been a topic of debate and has been attributed to many factors, including water-protein exchange or variations in magnetic susceptibility due to blood deoxy-hemoglobin, tissue lipid and non heme iron content. However, none of these factors can fully explain the observed phase changes due to demyelination or the lack of contrast between white matter (WM) and cerebro-spinal fluid, which, in fact, have very different magnetic susceptibilities. He and Yablonskiy recently demonstrated that the phase contrast of MRI signal depends on the tissue architecture [1]. In normal human brain white matter, myelin sheaths are arranged in a highly anisotropic manner. On the other hand, grey matter (GM) does not have a preferred fiber orientation which means that it has an isotropic structure. The same is true for MS lesions where part of the anisotropic myelin is transformed into myelin debris. The objective of this work is to investigate the relationship between tissue architecture and MR frequency shifts using numerical simulations and to compare the results with data acquired in 20 subjects with MS.

Methods: Using numerical simulations we investigate what happens with the MR signal when one part of a normally anisotropic WM tissue within an imaging voxel changes its architecture from anisotropic to isotropic. We assumed a two compartment model where the MR voxel contains tissue with a volume fraction λ which is isotropic and the rest of the voxel (1- λ) contains anisotropic tissue. The anisotropic fraction of the voxel consists of a simulated myelinated axon surrounded by WM tissue. The fiber direction is assumed to be perpendicular to the magnetic field. The reason for this is purely geometrical as, for any given direction, the number of fibre bundles is lowest parallel to that direction and increases with increasing angles. If the number of fibres was homogeneously distributed over the whole solid angle of 4π, the number of voxels belonging to fibres with an angle Θ would be proportional to sin Θ. The phase for the isotropic part is derived from the frequency shift given by the conventional formula for isotropic tissue (eq. 1). The phase for the anisotropic tissue is derived from the frequency shift formula provided by He and Yablonskiy for WM tissue [1] (eq. 2). A WM myelin content of 10% was assumed. χ_{wm} is the magnetic susceptibility of white matter and χ_a is the magnetic susceptibility of the axon which is assumed to be the same as the magnetic susceptibility of lipids since myelin is mainly composed of lipids. Θ is the angle between the fiber direction and the magnetic field and f0 is the resonance frequency at B0. The structural change from anisotropic to isotropic is simulated under the assumption that the fraction of myelin transforming from healthy anisotropic to isotropic myelin debris is proportional to the fraction of healthy myelin. This results in an exponential decay of myelin. The net signal from a voxel was computed as the complex sum of the signals emitted by the two compartments. The angle of the total signal at TE=20 ms corresponds to the phase of the images. The simulation was compared to data acquired from 20 subjects with relapsing-remitting MS (15 female, 5 male; median EDSS = 2.5 (range 1.0-6.0); mean age = 40yrs (range 28-57yrs); mean disease duration = 8.5 yrs (range 0.5-27yrs)) were scanned at 1 month intervals over 6 months on a Philips Achieva 3.0T system. Phase data were acquired with a flow-compensated 3D gradient echo method [2] (TR/TE/alpha=40/20/19, acquisition matrix = 480 x 231 x 32, reconstruction matrix 560 x 560 x 64). Phase images were unwrapped [3] and high pass filtered.

$$\frac{\Delta f_{iso}}{f_0} = \frac{4}{3}\pi\chi_{wm} \quad (1)$$

$$\frac{\Delta f_{aniso}}{f_0} = \frac{4}{3}\pi\chi_{wm} - 2\pi\chi_a\left(\cos^2\theta - \frac{1}{3}\right) \quad (2)$$

Results: The phase of the signal resulting from the numerical simulations is plotted against a time of four months (fig1). The phase decreased over time as the tissue structure changed from anisotropic to isotropic. This structural change is used to model the demyelination process that happens in MS lesions. The average phase of the 29 lesions found in the data collected from the 20 subjects is plotted against a time duration of 7 months, where month 1 corresponds to the month that the lesion appeared and was detected (fig 2). The decrease in phase after enhancement is similar to the prediction of the two compartment model. Fitting the model to the acquired data results in a characteristic time of myelination of 0.5 months and a myelin fraction in the voxel of 0.25.

Discussion and conclusion: Changes in tissue architecture from healthy anisotropic to demyelinated isotropic WM resulted in an exponential decrease in MR signal phase. A decrease in phase over the course of time after a lesion appears is also observed in the data collected which supports the validity of the simulated model and the underlying assumptions. The increase in phase observed by the data after the fourth month could be attributed to remylination which our model does not account for. Our data supports He and Yablonskiy's interpretation of phase contrast being also caused by differences in tissue architecture. The characteristic time of demyelination is in good agreement with serial studies using magnetization transfer [4] and diffusion MRI [5].

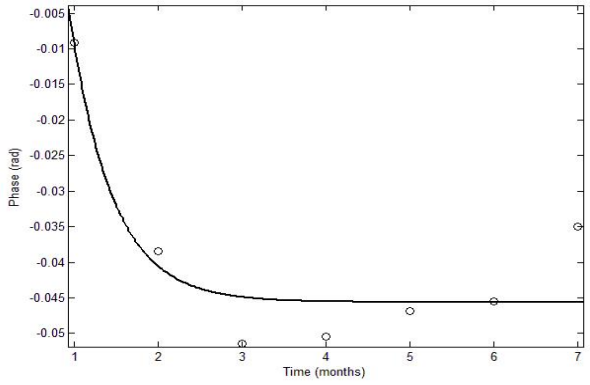

Fig. 1: The graph shows the average phase starting at the time of enhancement where the phase is close to 0 (rings). Our model fitted to the acquired data results in an exponential function with a characteristic time of demyelination of 0.5 months and a myelin fraction in the voxel of 0.25.

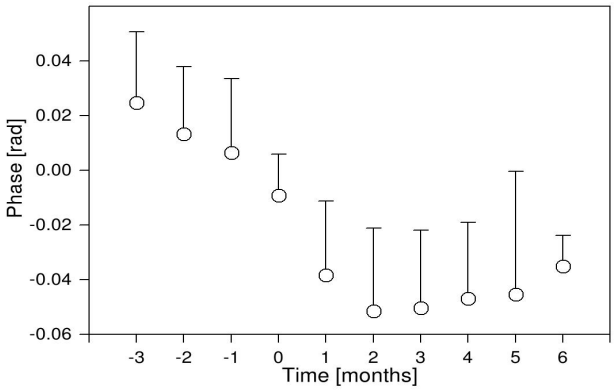

Fig.2: Average phase over 29 new regions found in the 20 subjects. Over the period of the study 29 new lesions were identified by gadolinium enhancement. The lesion appears at month 0, averaged over all 29 lesions. At the time of enhancement (month 0) the phase is close to 0. The phase reaches a minimum about two to three months after enhancement.

References:
[1] He and Yablonskiy DA; PNAS 2009 [2] Reichenbach JR, Venkatesan R et al. Radiology 1997 [3] Witoszynskyj S, Rauscher A et al. Medical Image Analysis 2009. [4] Laule C, Vavasour I et al. J Neurol 2003 [5] Fox RJ, Cronin T et al. AJNR 2010