Orientation Dependence of Magnetization Transfer in Human White Matter.

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Introduction. Detailed information about macromolecules could be most valuable for a better understanding of tissue composition. Information about macromolecules can be obtained from magnetization-transfer (MT) experiments using off-resonance saturation of the broad macromolecular resonance line and observation of the effect on the free water pool [1]. Another aspect of microstructure is orientational anisotropy of tissue parameters. Variation of the signal intensity depending on orientation with respect to the main magnetic field, $\mathbf{B}_0$ ('magic angle effect') has been recently demonstrated for peripheral nerve tissue [2]. In the current study, we investigated the orientational dependence of quantitative MT (*q*MT) parameters.

Theory & Methods. Experiments in a healthy volunteer were performed at 3T (Magnetom TIM Trio, Siemens, Erlangen, Germany) using a 32-channel head array. Measurements comprised a DTI scan (twice-refocused spin-echo EPI, TE 100 ms, TR 2s, matrix 128×128, 60 diffusion-encoding directions, b = 1000 s/mm²), an MT-prepared gradient echo acquisitions (10ms Gaussian off-resonance pulse with 300Hz bandwidth followed by a spoiler gradient and a 2.1ms sinc readout pulse, TR 31.3 ms), and a fieldmap scan. For the saturation pulse, a total of 17 off-resonance frequencies, logarithmically distributed between 50 Hz and 40 kHz, and 3 amplitudes were used. Steady-state like conditions were reached after 7s of dummy cycles. Subsequently, 8 repetitions were averaged. The fieldmap was used for correcting spatial distortions of the DTI images and for considering the effect of field inhomogeneities on the off-resonance frequencies in the MT parameter estimation. MT parameters were extracted employing a complete description of the pulse sequence by solving the McConnell equations numerically using matrix algebra [3, 4]. The standard two-pool model consisting of a liquid pool, a, and a semi-solid pool, b. A Lorentzian lineshape was assumed for the liquid pool and a super-Lorentzian lineshape for the semi-solid pool. The timing of the pulse sequence and the exact pulse shapes were stored in a protocol file to ensure a comprehensive and precise simulation of the pulse sequence. Fitting was performed using a Levenberg-Marquardt algorithm with 5 parameters: T_{2b} (the transverse relaxation time of the semisolid pool); $M_{0b}{\cdot}T_{1a}$ (the pool size of the semi-solid pool weighted by the longitudinal relaxation time of the liquid pool); (T_{1a}/T_{2a} the ratio of the relaxation times of the liquid pool); R (a pseudo first-order rate constant describing exchange processes between both pools), and G (a scaling factor [5]). T_{1b} was set to 1s as proposed in [1]. Form DTI data, the angle θ between $\mathbf{B}_0$ and the principle axis of the diffusion tensor reflecting the fiber orientation was extracted. The fractional anisotropy (FA) was used to identify voxels with a well-defined fiber orientation. Voxels with an estimated error in T_{2b} >20% were excluded from the final analysis of potential orientation effects, which was further restricted to voxels with FA=0.6…0.95.

Results. By using a comprehensive model for parameter fitting, high quality parameter maps were obtained. Figs. 1a and b show the T_{1a}-weighted size of the semi-solid pool and the relaxation time T_{2b}, respectively. Noticeable, T_{2b} shows structural information complementary to the pool size contrast. For instance, the splenum of the corpus callosum (cc) has reduced signal intensity on the T_{2b} map (Fig. 1b). Fiber orientations are shown in Fig. 1c. The normalized signal intensity as obtained from the MT experiment is shown in Fig. 2a as a function of the off-resonance frequency. Two regions of interest were selected: A region in the cc (ROI1, red) and a region located in the underlying white matter (WM) of retrosplenial cortex (ROI2, blue) with θ ≈ 80° for ROI1 and θ ≈ 10° for ROI2. It is obvious that M_z/M_0(ROI2) > M_z/M_0(ROI1) for all off-resonance frequencies beyond 1 kHz. This behavior is caused by a higher saturation rate of the semisolid pool observed in the cc (ROI1). The increased saturation rate results from a broader lineshape corresponding to the shorter T_{2b} in this region. The direction dependence is seen more noticeable by a voxel by voxel plot of T_{2b} as a function of θ (Fig. 2b).

Fig 1: (a) T_{1a}-weighted pool size of the semisolid pool; (b) T_{2b} of the bound pool; (c) color-coded FA map showing perpendicular fiber orientation in ROI 1 and parallel fiber orientation in ROI 2 corresponding with low and high T_{2b} values, respectively.

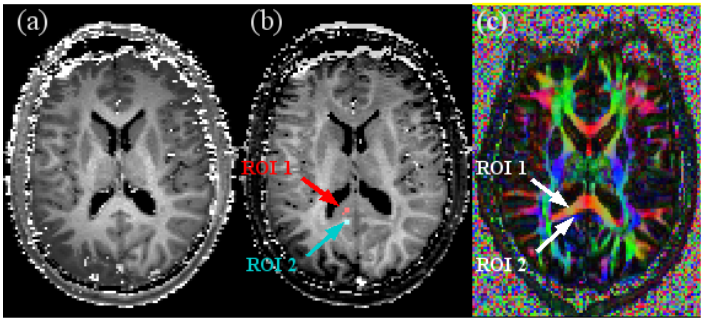
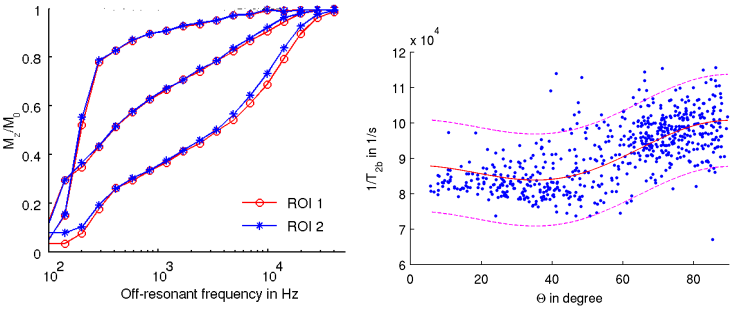


Fig 2: (a) Signal intensity in ROI1 and ROI2 plotted as a function of the off-resonance frequency and amplitudes; (b) dependency of $1/T_{2b}$ on the angle θ. The red line shows a fit to $(1/T_{2b}') + \kappa\,(3\cos^2\theta_n\text{-}1)^2$ and its 95% confidence interval (assuming $\theta_n = 90°\text{-}\,\theta$).



Discussion. The major finding is a noticeable correlation between the diffusion-tensor orientation and the transverse relaxation rate (i.e., the linewidth) of the semi-solid (i.e., macromolecular) pool (Fig. 2b). So far, a stringent explanation of this effect cannot be given. However, if one assumes that the lipid bilayer of the myelin sheath can be characterized to be liquid-crystalline, a reasonable estimation is obtained. In the liquid-crystalline phase, intermolecular dipole-dipole interactions are reduced to a negligible amount by radial diffusion, while fast axial rotation reduces the intramolecular dipole-dipole interactions and causes the angular dependence of the Hamiltonian to be the same for *all* protons [7-8]. Thus, the line shape is independent of θ_n, the angle between the bilayer normal vector and $\mathbf{B}_0$. The effect of a variation of θ_n is only a change in frequency scale since the couplings between all protons are multiplied by the same factor, ½ $(3\cos^2\theta_n\text{-}1)$. This causes the super-Lorentzian lineshape that is observed for liquid-crystalline samples [7]. It was shown, that the above assumptions are fulfilled for lipids, cholesterol and also for peptides in or attached to lipid bilayers in many model-membrane systems [7-11]. The assumptions about molecular motions are, to some extent, also valid for WM, which is reflected in the fact that the lineshape of the macromolecular pool is well described as a super-Lorentzian [12]. If the largest component of the diffusion tensor and, hence, the direction of the axon is aligned parallel to $\mathbf{B}_0$ the direction of the bilayer normal will always be perpendicular to B_0. Therefore, dipole-dipole couplings in the spin-system of the lipid bilayer are scaled by a factor of −1/2. Consequently, the NMR linewidth of the bilayer will be reduced if its normal is oriented perpendicular to $\mathbf{B}_0$. On the contrary, if the axon is aligned perpendicularly to $\mathbf{B}_0$, the orientations of the respective bilayer normals are evenly distributed, resulting in a broader linewidth. Although a full explanation of these effects is not obtained from these simplifying assumptions, it is reasonable to assume that at least parts of the macromolecular pool have liquid-crystalline characteristics and that the effect is partially related to partially averaged dipole-dipole interaction in liquid-crystalline systems.

References. [1] Henkelman RM, MRM 1993; [2] Chappell KE, AJNR 2004; 25:431. [3] Helgstrand M, JBNMR 2000;18:49. [4] Müller DK, ISMRM 2009;4470.; 58: 144. 29: 759. [5] Ramani A, MRI 2002; 20: 721. [6] Henkelman RM, MRM 1994 32:592. [7] Wennerström H, CPL 1972;18:41. [8] Forbes J, JACS 1988;110:1059. [9] Volke F, Pampel A., Biophys J 1995;68:1960. [10] Huster D., Prog Nucl Magn Res Spec 2005;46(2-3):79. [11] Davis JH, Biophys J 1995;69:1917. [12] Henkelman RM, MRM 1995 33:475.