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 anisotropy of tissue parameters. Variation of the signal intensity depending on orientation with respect to the main magnetic field, 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 (qMT) 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 consists 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 by solving the McConnell equations numerically using matrix algebra [3, 4]. The standard two-pool model consists 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 by solving the McConnell equations numerically using matrix algebra [3, 4].

Results. By using a comprehensive model for parameter fitting, high quality parameter maps were obtained. Figs. 1a and b show the T₁-weighted size of the semi-solid pool and the relaxation time T₁a, respectively. Noticeable, T₁b shows structural information complementary to the pool size contrast. For instance, the sphenum of the corpus callosum (cc) has reduced signal intensity on the T₁b 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 respect to the main magnetic field, B 0. 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 intraparticle 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, the angle between the bilayer normal vector and B 0. The effect of a variation of θ is only a change in frequency scale since the intervals between all protons are multiplied by the same factor, ½ (3cos²θ-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 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 B 0. On the contrary, if the axon is aligned perpendicular to 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.

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 intraparticle 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, the angle between the bilayer normal vector and B 0. The effect of a variation of θ is only a change in frequency scale since the intervals between all protons are multiplied by the same factor, ½ (3cos²θ-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 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 B 0. On the contrary, if the axon is aligned perpendicular to 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.