OBSERVATION OF MYELIN WATER AT ULTRA-SHORT ECHO TIME BY LONGITUDINAL RELAXOGRAPHIC IMAGING WITH SPIN-ECHO CENTER-OUT EPI (DEPICTING)

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Introduction: At low magnetic field ($\mathbf{B}_0$), longitudinal relaxation of the white matter (WM) ^1H_2O signal has been widely assumed mono-exponential as a result of effectively infinitely fast intercompartmental water exchange [1]. At 3T (Tesla), a smaller than expected fraction of myelin water is returned from analyses of inversion recovery (IR) data, while analyses of 7T data returns a value expected in human WM [2]. This suggests that water exchange between myelin *loci* and the neuron cytosol as well as between myelin *loci* and the inter-neuron space is not infinitely fast.

This is physically reasonable, since a $\mathbf{B}_0$-dependent shutter-speed (τ^{-1}) effect is consistent with the confined spaces between myelin membranes (*ca.* 2 nm in the myelin cell cytosol – oligodentrocyte tongue – and 3 nm between opposite exo-facial leaflets of myelin [3], **Fig. 1**). This facilitates frequent water exchange within myelin spaces, forming a "well-mixed" pool. *Ca.* 70% of intracellular and 47 % of extracellular myelin water is within 0.7 nm of a membrane surface [4]. Such biologically confined water has a freezing temperature below that of bulk water and can be separately observed [1]. A recent study suggests that unfrozen water is part of the slow diffusing component detected in bi-exponential diffusion [5]. The time required for circumferential diffusion of water in myelin *loci* could be greater than 600 ms given the apparent diffusion coefficient of the slow diffusing component. All of this means that the intrinsic myelin space ^1H_2O T_1 should increase less with $\mathbf{B}_0$ than the neuron cytoplasmic and inter-neuronal ^1H_2O T_1 values [6]. This results in an increased apparent longitudinal myelin water fraction because the resultant τ^{-1} increase causes the exchange to appear to slow down.

Myelin water has been widely observed by multi-exponential CPMG studies [7]. Determination of the ^1H_2O T_2 value associated with the short ^1H_2O T_1 component detected by IR relaxographic analysis would be of significant value to support the assignment as a myelin water fraction. The purpose of this study is to adapt a spin-echo center-out echo planar imaging with ultra-short echo time (DEPICTING [8]) pulse sequence to measure the ^1H_2O T_2 of the small ^1H_2O T_1 pool after an IR.

Methods: A volunteer (w 32y) gave informed consent for an examination at 3T (TIM Trio Siemens) with a circularly polarized coil. After shimming (Siemens WIP450) and a fieldmap scan, a series of 32 pseudo-randomized geometric TIs (25,37,51,…,6000 ms) were acquired with a DEPICTING readout [8] (**Fig. 2**): other parameters 90° binomial water selective excitation, spin echo refocusing at TE 7 ms, TR 10 s, 128×128 matrix, 192×192 mm^2 FOV, slice thickness 5 mm (**Fig. 3** left). Before varying TI, a second acquisition was performed with a TE of 20 ms. Total acquisition time of the fieldmap, template scan and two series of 32 TIs was 22 min. Effect of movement on IR series was estimated from the variation of the phase of the last 12 TIs and pixels with more than 2.5 degrees standard deviation were excluded, yielding an ROI of mostly WM (**Fig. 3** right). Cross-regularized inverse Laplace transformation [9] with 32 grids from 70 ms to 7 s was performed as described earlier [2]. The small relaxographic peak with small T_1 (*ca.* 80 ms attributed to myelin water, inset **Fig. 4**) was integrated at TE 7 and 20 ms and fitted to a mono-exponential transverse relaxation; the same procedure was applied to the larger peak with large T_1 (attributed to parenchymal WM).

Results: The T_2 histogram of the myelin water in WM exhibits a main peak at 34.2 (± 10.0) ms. The T_2 histogram of non-myelin water reveals a well separated peak at 73.2 (± 11.7) ms. These values are in excellent agreement with reported T_2 values of "water trapped between the bilayers of the myelin sheath" (10–50 ms) and of "intra/extracellular water" (70-90 ms) obtained by CPMG [7].

Discussion: Longitudinal relaxographic imaging of myelin water by echo planar imaging requires stable phase for the TI series. This limitation prohibited the study of gray matter, an aspect that may be improved by the implementation of adequate techniques to monitor head movements during the examination. The acceleration in acquisition time compared to PURR [2] enabled spin echo measurements at two TEs. Our results show that the T_2 of the IR-edited myelin ^1H_2O signal is in agreement with that of CPMG studies.

References: [1] Escanyé et al. 1984 *J. Magn. Reson.* 58:118. [2] Labadie et al. 2009 Proc. ISMRM p. 3652. [3] Min 2009 *PNAS* 106:3154. [4] Pal et al. 2002 *PNAS* 99:1763. [5] Dhital et al. submitted ISMRM 2011. [6] Rooney et al. 2007 *Magn. Reson. Med.* 57:308. [7] MacKay A. et al. 2006 *Magn. Reson. Imaging* 24 :515. [8] Hetzer et al. 2010 *Magn. Reson. Med.* in print. [9] Labadie & Jarchow 2004 Proc. ISMRM p. 2707.

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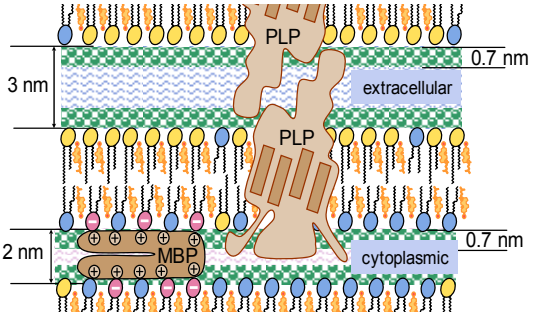

Fig 1: Cartoon of myelin membranes, having the water layer within 0.7 nm highlighted in green.

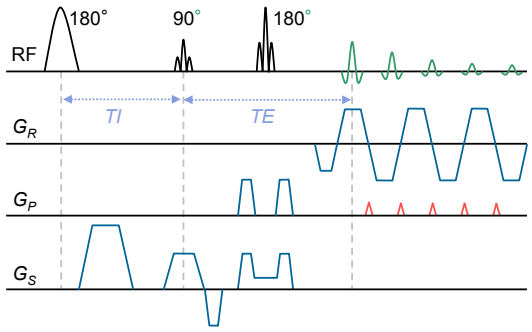

Fig 2: Adiabatic inversion followed by a spin-echo and a center-out EPI (DEPICTING), repeated to cover the second half of *k*-space. Timing of forward and reflected lines corrected with a template without phased encoding blips (red).

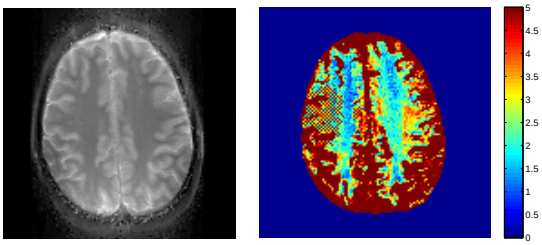

Fig 3: Image at TI 25 ms and TE 7 ms after multi-frequency reconstruction (left). Standard deviation map of the last 12 TI images at TE 7 ms (right), a threshold of 2.5 degrees was employed to select pixels with a stable phase (mostly WM).

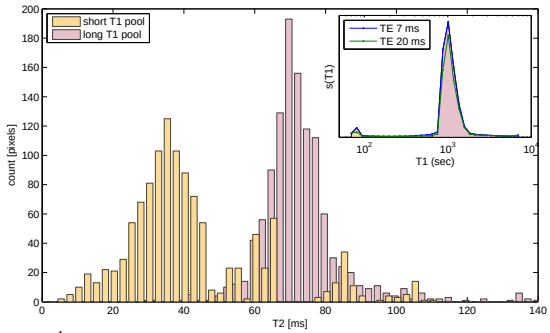

Fig 4: ^1H_2O T_2 histograms of the small and large WM pools with small and large ^1H_2O T_1 values. The small and large T_1 value pools exhibit T_2 histographic peaks at 34.2 (± 10.0) and 73.2 (± 11.7) ms, respectively. In the insert, the sum of the relaxogram of the selected voxels is displayed for TE 7 ms and 20 ms (myelin water forms a peak at ca. 80 ms).