Comparison of Myelin Water Fraction in Cross-Regularized T1-Relaxograms of Normal White Matter at 3T and 7T and of Normal-Appearing White Matter at 3T

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Introduction: The continuous distribution analysis (inverse Laplace transform, ILT) of inversion recovery (IR) human brain data acquired at 4T with a low flip angle (5°), short TE (ca. 8ms) and geometrically spaced TIs yields a T1-relaxogram that includes a small fraction of water relaxing with a short T1 (ca. 100-200 ms) [1]. The histogram of this water fraction exhibits a bimodal distribution corresponding to GM (ca. 5%) and WM (ca. 12%), which was attributed to the myelin water fraction (MWF) trapped between myelin bilayers [2]. At long TE (56 ms) and ultra short TIs (≥4 ms), Prantner et al. [3] detected a small (3.4%) rapidly relaxing component (44Hz) in rat gray matter due to cross-relaxation of water with immobile protons. The use of relatively long adiabatic pulses in human studies at high field prohibits such detection at ultra short TI. To minimize the effects of cross-relaxation at short TE (7 ms), we have suggested performing an ILT based estimation of the inversion efficiency prior to the analysis [4]. In this study, we explore the MWF in IR brain data from a volunteer at 3T and 7T and in the NAWM of an MS-patient at 3T.

Methods: *PURR sequence* [5]: Look-Locker IR sequence implemented under Siemens VB15-IDEA with a non-selective adiabatic pulse (SBBIrNs), 32 FLASH 5° read-outs, TE 7ms, 150Hz/Px, on a 3T Siemens TimTrio (12-channel coil with adaptive combination) and a 7T Siemens scanner (8-channel coil). *Processing*: individual channel raw-data (twix) were reconstructed (ODIN, od1n.sourceforge.net [6]) and pixel-wised phased (average phase of the 4 first and 4 last TIs). The real part of each channel was linearly combined and the IR curve of each pixel submitted to a cross-regularized ILT [7] with 32 T1 grids logarithmically spaced between 70ms and 7sec using CONTIN [8] after estimation of the inversion efficiency (smoothed with a 5mm FWHM). *Volunteer*: 21-yr female. *Patient*: 23-yr female with mild relapsing-remitting MS (several supratentorial plaques, one infratentorial lesion, CSF positively tested for oligoclonal bands, EDSS score 2.0, 5 yr since initial diagnosis, 4 yr Interferon beta-1a Avonex treatment, in last 2 years slow progression with at least 3 new minor lesions).

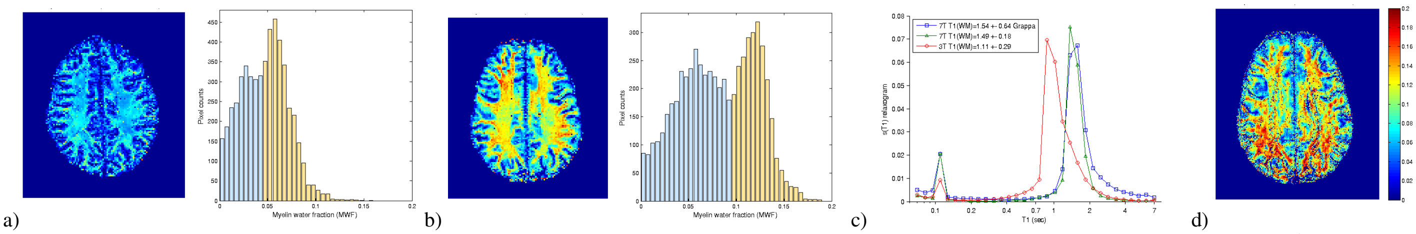

Fig. 1: **a)** Map of the myelin water fraction (MWF) and corresponding MWF histogram of a healthy subject at 3T, single 112×128 slice, 1.6×1.6×5 mm^3, geometrically spaced Look-Locker $TI_1/TI_2/TI_{16}/TI_{32}$/TR=16.46ms/30.46ms/717.46ms/7.99sec/15sec, **b)** MWF map of the same subject at 7T, **c)** white matter T1-relaxograms at 3T and 7T corresponding to the sum of pixels with higher MWF (peak highlighted in yellow in the a) and b) histograms), **d)** same slice as in b) at 7T but acquired with a 224×256 matrix, 0.8×0.8×5 mm^3, GRAPPA with acceleration factor 4 and 32 reference lines (GRAPPA weights were computed in the last TI image with ODIN).

Results & Discussion: The MWF map was computed pixel-by-pixel by integrating the area of the small T1 peak at ca. 105 ms (see T1-relaxograms in Fig. 1c) divided by the total water relaxogram. The average MWF in white matter increased from 3T (0.073 ± 0.014) to 7T (0.132 ± 0.013). Although the T1 of the main peak, corresponding to water in axons, glial cells or extra-cellular, increased from 3T (1.114 ± 0.293 sec) to 7T (1.493 ± 0.177 sec), that of the myelin water remained relatively unchanged at 3T (110.0 ± 15.8 ms) and 7T (105.5 ± 7.2 ms). Assuming that the T1 of gray matter pixels, in which the MWF was near null, is representative of the T1 of axons in white matter in absence of water exchange with myelin, a two-site-exchange fit was attempted and returned a residence time of water in myelin of 666.4 ± 369.5 ms and a fraction of myelin water of 0.158 ± 0.104. This apparent slow exchange is in agreement with both previous diffusion data of rat brain [9] and earlier neutron diffraction studies of highly myelinated nerves in which the kinetics of hydrogen-deuterium exchange at 6°C ranged from 6 to 12 min [10], suggesting that the diffusion of water between bilayers is hindered (e.g. by proteins involved in myelin compaction, the extracellular proteolipid protein PLP of the intraperiod lines, and the intracellular myelin basic protein MBP of the major dense lines). The two-site-exchange model may not account for the complex pathways of water transport between intra-axonal and glial cells as required by homeostatis, in particular in the peri-axonal non-compact myelin and through gap-junctions in the para-nodal loops (see Fig. 12 in [11]). The inversion efficiency might not be comparable in the axon and in myelin, where water is more closely in contact with membranes of the bilayers, an aspect that may affect the results of the two-site exchange fit. Yet the apparent long residence time in myelin may explain the observation of a myelin water fraction. Our previous results at 4T and the present work suggest that the detection of the MWF is facilitated at higher fields, and may approach the expected value of 0.15 at 7T. The total acquisition time may be reduced or the image resolution increased with GRAPPA acceleration but at the cost of SNR and of the estimation of the inversion efficiency which leads to an underestimation of the MWF in gray matter (Fig. 1d).

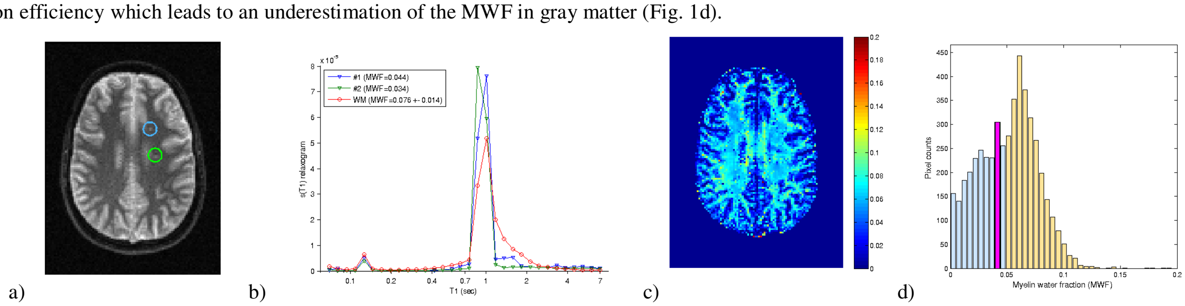

Fig. 2: **a)** PURR image TI 250 ms at 3T of an MS-patient, single 96×128 slice, 1.7×1.7×5 mm^3, $TI_1/TI_2/TI_{16}/TI_{32}$/TR=17ms/31ms/719ms/9sec/12sec, **b)** T1-relaxogram of lesion #1 (blue circle) and of lesion #2 (green circle) and of white matter, **c)** MWF map, **d)** MWF histogram with a slightly increased MWF at ca. 0.0416.

The T1-relaxograms (Fig. 2b) of the lesions of the MS-patient reveal a main T1-peak for lesion #1 (1.097 sec, blue curve) and lesion #2 (1.024 sec, green curve) overlapping with that of white matter (T1 of main peak at 1.13 ± 0.36 sec, red curve). However, their MWF is lower than that of white matter, respectively 0.044 and 0.034 instead of 0.075 ± 0.014. It is worthwhile noting that the histogram of the MWF exhibits a slight increase at an MWF of ca. 0.04. This preliminary study suggests that further investigations in NAWM may help to characterize the behaviour of the T1-based MWF during the course of the disease.

References: [1] Labadie C 2007 *P. ISMRM* 15:2106 [2] Labadie C 2008 *P. ISMRM* 16:2243 [3] Prantner AM 2008 *MRM* 60:555 [4] Labadie C 2008 *P ISMRM.* 16:1418 [5] Labadie C 1994 *JMR B* 105:99 [6] Jochimsen TH 2004 *JMR* 170:67 [7] Labadie C 2004 *P ISMRM* 12:2707. [8] Provencher SW 1982 *Comp. Phys. Comm.* 27:229 [9] Meier C 2003 *MRM* 50:510 [10] Kirschner DA 1976 *Brookhaven Symposia in Biology* 27:R68 [11] Kamasawa N 2005 *Neuroscience* 136:65

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