

Evidence of the myelin origin of the short T_2^* component in white matter: a combined magnetization transfer and T_2^* relaxometry experiment in the marmoset brain at 7T

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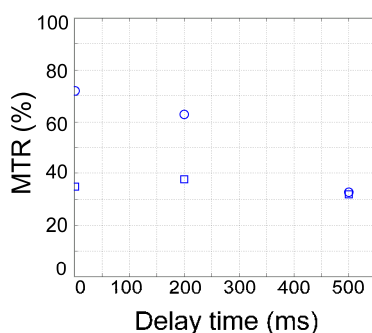
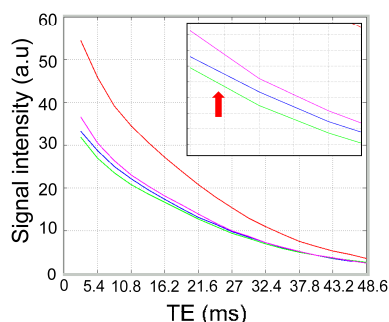
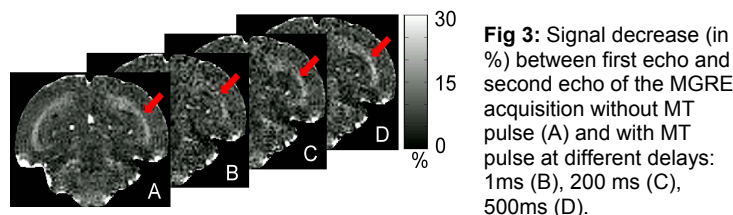
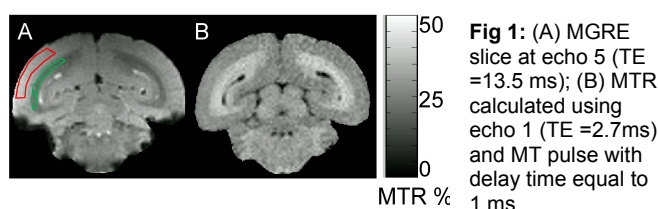
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Introduction: Assessing non-invasively the myelin inside the brain has been a longstanding goal of MRI, as it may aid the study of demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis. Interestingly, recent gradient-echo studies suggest a multi-component T_2^* decay in white matter (WM) fibers of human brain [1,2], with the existence of a short component (few ms) tentatively attributed to water protons trapped inside myelin [3]. To further investigate the origin of this short T_2^* signal, we performed a combined magnetization transfer and T_2^* relaxometry experiment at 7T in marmoset brain, an excellent *in vivo* model for investigating T_2^* -based MRI [4]. The rationale was that if the short T_2^* component originates from myelin water, its MT effect should show a dependence on delay that is distinctly different from that of other water compartments, reflecting the restricted exchange that has been previously observed between the various water pools in white matter [5,6].

Materials and Methods: *In vivo* brain imaging of an anesthetized marmoset was done on a 7T/30cm MRI scanner (Bruker-Biospin) using a custom-built birdcage transmission coil and a phased-array receiver coil. A single coronal slice through the optic radiations of the marmoset was acquired using a multi-gradient-echo (MGRE) sequence. The shortest echo time was 2.7 ms and the longest 48.6 ms, for a total of 18 echoes spaced at 2.7 ms. Other parameters: repetition time = 2500 ms, flip angle = 90 degrees, voxel resolution = $300 \times 300 \times 600 \mu\text{m}^3$, number of averages = 3. Time-dependent MT experiments were performed involving a brief (100 ms) and intense MT preparation, a varying delay, and a subsequent multi-gradient echo (MGRE) readout. Therefore, the MGRE acquisition was repeated with a preparation magnetization transfer (MT) segment (two 50 ms Gaussian pulses at 2 kHz positive offset from the water resonance with maximum B_1 of 22.5 μT) using three different delay times between MT pulse and MGRE sequence (1 ms, 200 ms and 500 ms). Regions of interest (ROIs) in the optic radiations (OR) and cortical gray matter (GM) were drawn manually. Similarly to the human study [1], a three-component model allowing for a variable offset frequency of the components was used to fit the T_2^* decay curves of the ROIs. Magnetization transfer ratios (MTRs) were then calculated on a pixel-by-pixel basis, as well as for the short and medium T_2^* components averaged across the optic radiations, using $\text{MTR} = (1 - M_s/M_0) \times 100$ where M_s and M_0 are the intensities acquired with and without an MT pulse, respectively.

Results/Discussion: The ROIs drawn for the optic radiations (green) and cortical gray matter (red) are represented on the MGRE slice (Fig 1A). The three-component analysis of the T_2^* relaxation curve in the optic radiations revealed a multi-exponential decay with two dominant contributions from short ($T_2^* \sim 6$ ms) and medium ($T_2^* \sim 22$ ms) components. Whereas the cortex showed only a mono-exponential decay ($T_2^* \sim 30$ ms). Similarly to the human brain, the rapidly relaxing component ($T_2^* \sim 6$ ms) of the optic radiations had an amplitude of $\sim 12\%$ relative to the total signal (against $\sim 80\%$ for the medium component) and displayed a substantial resonance frequency shift relative to the medium component, reaching up to 50 Hz. The use of a preparation MT pulse had a strong effect on the signal intensity of optic radiation fibers (MTR $\sim 35\text{--}40\%$, Fig 1B) as well as on the shape of its T_2^* relaxation curve (Fig 2). More particularly, the early part of the decay of the optic radiations was significantly reduced by the MT pulse with the shorter delays and recovered as delay time was increased (red arrow in magnified view of Fig 2). This is further illustrated by the relative signal decrease between the first and second echo of the MGRE acquisition; this decrease is smallest for the 1 ms MT-pulse delay, indicating the relative absence of a short T_2^* component (Fig 3). Using the amplitudes obtained from the three-component analysis at short delays (1 ms and 200 ms), the MTR of the short T_2^* component was found to be much larger than the MTR of the medium T_2^* component delay (Fig 4), indicating a closer association (and very fast exchange) of the water protons from the short T_2^* component with the motionally restricted non-aqueous protons. On the other hand, the MTRs of both T_2^* components were similar at long delay (500 ms), suggesting that exchange also occurs between the two water protons pools (short and medium) and may be more rapid than 500 ms. These results are in agreement with previous work done on the short and long T_2 components of the human WM at lower field strength [6]. Note that the MT pulse also had a significant effect on the signal intensity of the cortical gray matter (MTR $\sim 25\text{--}30\%$ in Fig 1B), but no effect was detected on the shape of its T_2^* relaxation curve (not shown here).

Conclusions: The results obtained in the marmoset brain at 7T indicate the short T_2^* component in WM comes from water protons in close interaction with motionally restricted non-aqueous protons from myelin bilayers (lipids and proteins). Additional work is currently underway to further explore this short signal T_2^* as a potential *in vivo* marker of myelin at ultra-high field.



References: [1] Van Gelderen *et al.*, MRM (2011); [2] Du *et al.*, MRM, 58:865–870 (2007); [3] Laule *et al.*, Neurotherapeutics 4:460–84 (2007); [4] Sati *et al.*, Neuroimage (2011); [5] Stanisiz *et al.*, MRM 43:1128–1136 (1999); [6] Vavasour *et al.*, MRM 44:860–866 (2000).