Magnetization Transfer from Inhomogeneously Broadened Lines (ihMT): sequence optimization for preclinical investigation at very high magnetic field (11.75T)

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Target audience: MR physicists and biologists interested in novel endogenous contrast mechanisms and myelin imaging

Purpose: Inhomogeneous magnetization transfer (ihMT) imaging has been recently proposed as new technique for white matter imaging[1,2]. Inhomogeneous broadening of a resonance line may occur in semi-solids whose proton magnetization does not exchange rapidly throughout the molecule. Lipid bilayers, specific components of myelin, presumably present such characteristics and hence ihMT has shown tremendous specificity for myelinated structures[1]. IhMT, as a myelin specific imaging technique, would represent a precious asset to assess myelin content and integrity in preclinical models of human brain diseases (e.g. Multiple Sclerosis). Whereas preclinical feasibility of ihMT has been demonstrated[3,4], optimization of the resulting signal and contrast is required. This constituted the subject of this work, which presents optimization of a 2D pulsed ihMT technique for preclinical investigation at very high magnetic field.

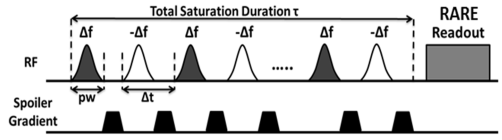

Fig.1 : ihMT preparation ;case of dual frequency saturation

Method: Experiments were performed on a Bruker Avance 500 MHz/89 mm wide bore vertical imager (Bruker, Ettlingen, Germany) on anaesthetized healthy mice (n=3, body temperature maintained at 36.3±0.3°C). A pulsed saturation preparation scheme[4] was combined with a turbo spin echo readout module (RARE, slice thickness=1mm, FOV=25x25 mm, Mtx=64x64, TE=1.82 ms, TR=3.4 s). IhMT images were generated by combining 4 different single and dual frequency offsets saturated MT images (Fig 1) as previously described in 1 and 2. 30 NEX (acq. time 6 minutes) of each MT image were acquired to increase the SNR. An additional unsaturated image was acquired to derive quantitative ihMT ratios (ihMTR). Measurements (mean±standard deviation) were performed in ROIs selected in internal capsule (IC), corpus callosum (CC), cortex gray matter (cGM) and muscle (Mu, Fig. 3). Optimization was focused on the following parameters of the ihMT preparation: pulse width (pw), interpulse repetition time (ΔT), integrated squared B_1 (proportional to energy deposition, defined as $Etr=B_1^2.\tau$, where τ is the duration of the saturation train) and frequency offset values (Δf). A fixed τ value of 900ms was used in this study. Each parameter was varied independently keeping other parameters constant. Two criteria were considered: sensitivity measurement (ihMTR values) and specificity (characterized by the contrast between myelinated structures (e.g. IC and CC) and non-myelinated structures (e.g. muscle)).

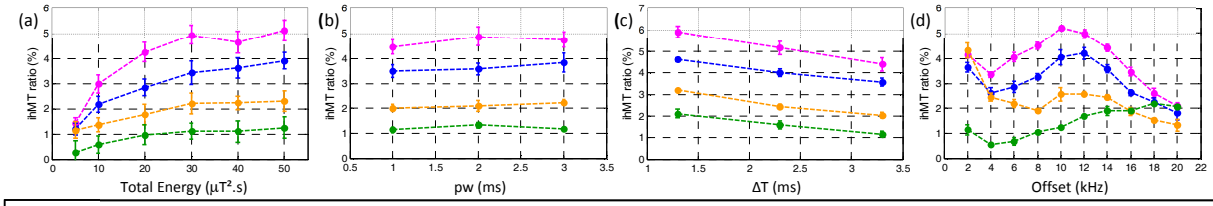

Fig.2: ihMTR values as a function of Etr, (for pw/ΔT=3/3.3ms, Δf=±10kHz) (a), pw (for ΔT=3.3ms Δf=±10kHz, Etr=40μT².s) (b), ΔT (for pw=1ms, Δf=±10kHz, Etr=40μT².s) (c) and Δf (for pw/ΔT=3/3.3ms, Etr=40μT².s) (d).

Results and Discussion: Mean ihMTR values, measured in IC (pink curves), CC (blue curves), cGM (orange curves) and Mu (green curves) as a function Etr (a), pw (b), ΔT (c) and Δf (d), are reported on Fig 2. IhMTR values increased quickly with increasing energy deposition (Fig. 2a) then tended to saturate at higher level (ihMTR=5% for Etr>30 μT².s). Of interest, this behavior was similar to that observed in humans at 1.5T and 3T[2,5] and for the similar Etr levels. Whereas pulse duration demonstrated little effect on ihMTR variations (Fig 2b, similar ihMTR values for pw=1, 2 or 3ms), the interpulse repetition time appeared to be a crucial parameter. As shown on Fig 2c, the faster the RF pulses were repeated, the higher the ihMTR value (e.g. in IC, ihMTR=6% for ΔT=1.3ms, decreasing to 4.8% for ΔT=3.3ms). This behavior is actually expected from theoretical considerations since inhomogeneous components of the spectrum would tend to homogenize for long mixing times (in human brain, the exchange time associated with inhomogeneous component is ~7ms[6]). Hence, short ΔT (i.e. fast dual-frequency saturation switch and consequently, reduced mixing time) is required to reveal signal from inhomogeneously broadened lines. Of importance, decrease of ΔT did not affect ihMT ratios of all structures similarly: +25% for IC, and +200% for Mu, for ΔT varying from 3.3ms to 1.3ms. Therefore, at ΔT=1.3ms, significant signal from muscle was evidenced and a loss of specificity for myelinated structures was noticed ($ihMTR^{IC}/ihMTR^{Mu}$=6.0/2.0=3.0 for ΔT=1.3ms as compared to $ihMTR^{IC}/ihMTR^{Mu}$=4.8/1.0=4.8 for ΔT=3.3ms). A ~10kHz offset frequency corresponded to the peak ihMTR values for brain IC and cGM. A slight shift for CC could be noticed, with a maximum ihMTR value obtained for Δf=12kHz (Fig. 2d). The slight difference in optimal Δf values for IC and CC could suggest sensitivity of ihMT to the WM fiber orientation anisotropy (perpendicular to B_0 for CC, parallel to B_0 for IC).

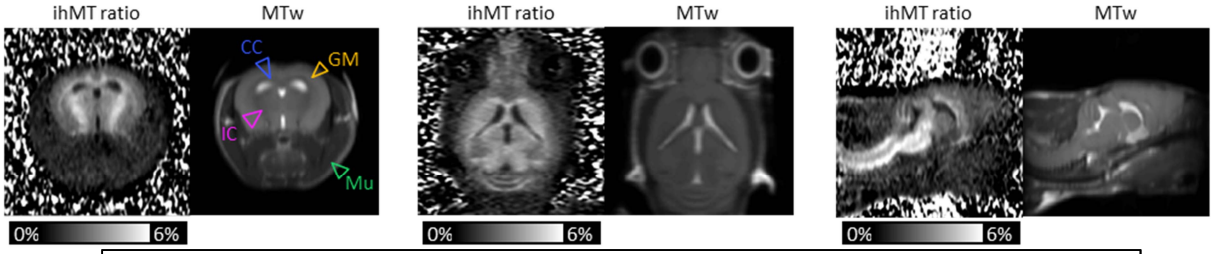

Fig. 3: axial, coronal and sagittal MT(+Δf) weighted and ihMTR images obtained for Δf=±10kHz, Etr=40μT².s, pw/ΔT=3/3.3ms and showing specificity for myelinateds structures.

Conclusion: This study focused on optimizing a pulsed ihMT preparation module for preclinical applications at very high magnetic field (11.75 T). The following set of parameters, Δf=10kHz, Etr>30μT².s and pw/ΔT=3/3.3ms, represented the best trade-off between sensitivity and high specificity for white matter (Fig. 3), leading to ihMTR values of ~5% in IC, ~4% in CC, ~2% in cGM and <1% in Mu. Although the general behavior of ihMT with energy of saturation and timing parameters was similar to that of human studies[2], absolute ihMTR values in mouse brain were roughly twice as small as for human brain. Whereas it cannot be excluded that myelin composition and structure differ between mice and humans, anesthesia effect on lipid membranes may also alter the exchange processes associated with inhomogeneous lines. This should be further investigated. Nonetheless, the optimized sequence in its present form is able to provide semi-quantitative information regarding myelinated structures and could be incorporated in multimodal MR protocols dedicated to study mouse models of brain pathologies.

References: [1] Varma *et al*, Magn Reson Med (2014), [2] Girard *et al*, Magn Reson Med (2014), [3] Duhamel *et al*, Proc. ISMRM2013 (#2506), [4] Prevost *et al*, Proc. ISMRM2014 (#1498), [5] Girard *et al*, Proc ISMRM2014 (#4236), [6] Varma *et al*, Proc ISMRM2013 (#2536)