Magnetization Transfer from Inhomogeneously Broadened Lines (ihMT): Qualitative Evaluation of ihMT Specificity toward Myelinated Structures

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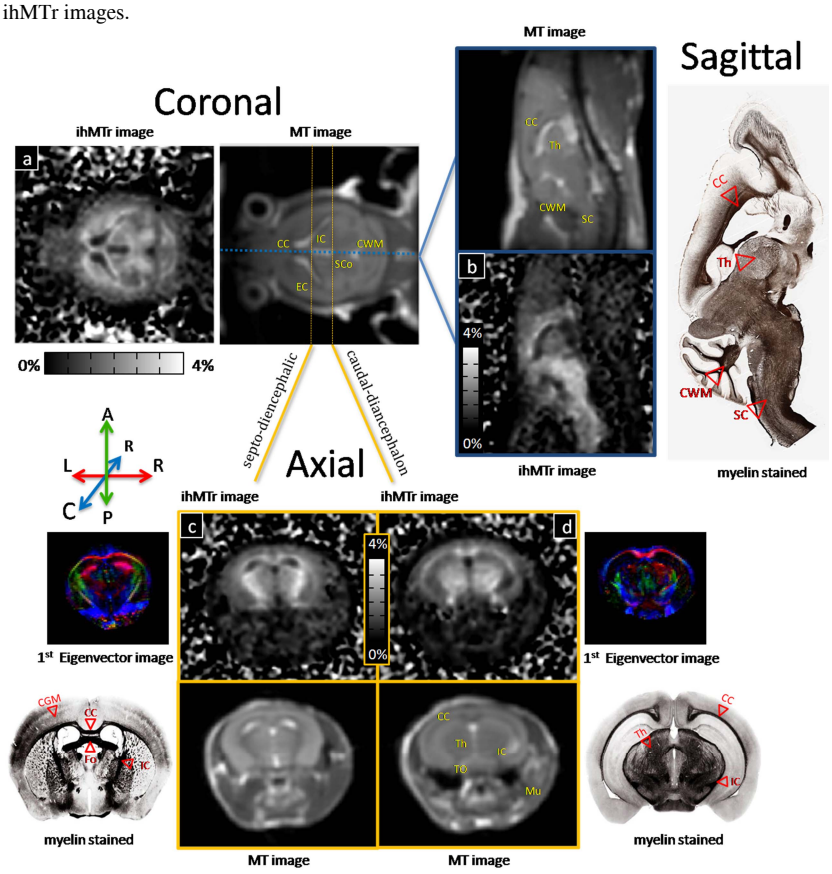
Target audience: MR physicists and physicians interested in novel endogenous contrast mechanisms and specific white matter imaging.

Introduction: Specific imaging able to provide quantification of myelin concentration is a real challenge and a very active research area as it would be valuable for clinical and preclinical studies of white matter pathologies. While several advanced MR techniques are used to assess myelin content (Myelin Water Fraction, quantitative Magnetization Transfer (qMT), Diffusion Tensor imaging (DTI)), they all are affected by confounding factors, which limit their specificity to myelin. On the other hand, a previously reported new MT approach able to specifically image the inhomogenous component of the MT spectrum, and referred as inhomogeneous MT (ihMT), appeared to be selectively sensitive to tissue with myelin [1-4]. Whereas several studies have been performed on humans at 1.5T and 3T and a preclinical feasibility study on mouse at 11.75T, the specificity of ihMT toward myelin has not been demonstrated yet. In this context, the main objective of our work is to use preclinical studies to demonstrate quantitatively the specificity of ihMT toward myelinated structures. As a first step, the present study proposed a qualitative investigation of ihMT specificity by comparison with DTI and myelin stained images.

Methods: Experiments were performed at 11.75T on a vertical MR system (Bruker, AV 500WB, transmit/receive volume coil: Ø 2cm, length 3cm) on anaesthetized mice (C57BL/6j, weight 25±1g). The ihMT preparation consisted in the acquisition of 3 MT images for which the saturation was performed with 3ms Hann-shaped off-resonance (±f=±8kHz) pulses applied every 3.3ms during 1200ms (total RF energy =25.17μT².s) and according to the scheme described in [1-4]. A multislice FSE readout module was used for imaging with the following parameters: mtx 64x64, FOV 2x2cm², TR/TE=3500/1.8ms, STH: 1mm (axial and coronal) and 0.75mm (sagittal). 128NEX were acquired to increase the SNR (total acq time: 32 minutes for each direction). M_0 signal was also measured to estimate ihMT ratio (ihMTr=ihMT/M_0). For comparison, axial DTI was also performed on the same mice, with a 2-shot SE-EPI sequence (12 directions, b=1200s/mm², TR=3s, respiratory gating). Finally, myelin stained images taken from http://mouse.brainarchitecture.org/ and http://www.hms.harvard.edu were used for qualitative comparison with ihMTr images.



		ihMTr (%)	% w/r CC
White matter	Corpus callosum (CC)	3,24	/
	Internal Capsule (IC)	3,58	+11%
	Tractus Opticus (TO)	3,93	+21%
	Fornix (Fo)	3,38	+4%
	External Capsule EC)	2,80	+13%
	Cerebelum (CWM)	3,44	+6%
	Spinal Cord (SC)	3,10	-4%
Grey matter	Thalamus (Th)	2,95	-9%
	Cortical Grey Matter (CGM)	1,95	-40%
	Superior Colliculus (Sco)	3,18	-2%
	Muscle (Mu)	0,69	-79%

Results and Discussion: The table shows ihMTr values (in %, left column) measured in various areas of the mouse central nervous system regions. The right column indicates the percentage of difference in ihMTr values with regards to the value in the corpus callosum, taken as reference. The figure showed typical MT weighted and ihMTr images obtained in each direction (a,b,c,d). High specificity of ihMT toward myelinated structures can be appreciated through different aspects: *i)* the absence of ihMT signal or weak ihMTr values in non-brain structures (e.g. muscle (ihMTr=0.69%), skin, eyes, fig a,b); *ii)* the good visual correlation in each direction between contrasts of ihMTr images and myelin stained images. These latters show highest myelin concentration in CC, IC, TO and CWM structures. SC also demonstrated high myelin concentration, whereas lower values are shown in cortical grey matter (CGM). Similar distribution was obtained for ihMTr values (ihMTr >3.2% in WM structures, ihMTr=3.1% in SC and ihMTr=1.95% in CGM); *iii)* the comparison of ihMTr with DTI images. Similarities are shown in areas of high WM anistotropy (e.g. CC (L-R direction), TO (R-C direction)), whereas differences are evident in crossing fibers areas (IC) and GM structures, both demonstrating little DTI signal but strong ihMT signal. This comparison indicated that ihMT and DTI contrasts are both sensitive to myelinated structures but arise from different mechanisms: WM anisotropy for DTI, myelin structure and density for ihMT. Contrasts obtained in the thalamus with the different modalities are also very representative. Thalamus is a grey matter structure but contains afferent axons non-preferably oriented. Consequently DTI anistropy maps showed a weak signal in this area whereas ihMTr values (fig b,d) were measured equal to ihMTr=2.95%, i.e. close to the value measured in SC (3.1%) or in CC (3.24%), which correlated qualitatively with the axial and sagittal myelin stained images.

Conclusion: Despite low spatial resolution (300x300μm²), the proposed ihMT technique allowed obtaining multislice images of mouse brain with clear enhancement of the myelinated structures in a reasonable scan time (30' per direction) and with a basic processing. Signal variations in the order of 3% were obtained in main WM structures. This ratio remained 3-4 times smaller than values obtained on humans with the same technique, indicating that improvement of the sensitivity might be possible and/or that confounding factors (e.g. anaesthesia effects, ultra high field effect) may occur. This preliminary qualitative work will serve as a basis for further studies dedicated to the quantitative demonstration of unique specificity of ihMT toward myelinated structures. This would be realized by correlating ihMTr with quantitative myelin stain analyses on both controls and mouse models of myelin disorders. However, based on the image quality obtained in this study, it is important to note, that although not fully characterized yet, the ihMT technique in its current state should be able to provide important information regarding myelin integrity in mouse models of WM diseases (e.g. EAE).

***References*: *[1]** Alsop et al, Proc. ISMRM 2005;p2224. **[2]** Girard et al, Proc. ISMRM 2013;p2506. **[3]** Duhamel et al, Proc. ISMRM 2013;p2535. **[4]** Varma et al, Magn Reson Med, in revision.*