Magnetization Transfer from Inhomogeneously Broadened Lines (ihMT): Application on a mouse model of experimental autoimmune encephalomyelitis (EAE)

Valentin H. Prevost[1], Angele Viola[1], Olivier M. Girard[1], Adriana T. Perles-Barbacaru[1], Jennifer Tracz[1], Gopal Varma[2], David C. Alsop[2], and Guillaume Duhamel[1]
[1]CRMBM CNRS UMR 7339, Aix-Marseille University, Marseille, France, [2]Departement of radiology, BIDMC, Harvard Medical School, Boston, MA, United States

Target audience: MR physicists and biologists interested in novel endogenous contrast mechanisms and specific 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, represents a precious asset to assess myelin content. Whereas preclinical feasibility of ihMT has been demonstrated[3,4], it sensitivity for myelin disorders pathology (e.g. multiple sclerosis (MS)) remains to be demonstrated. The chronic model of experimental autoimmune encephalomyelitis (EAE) induced with the MOG peptide is a recognized model of MS used in pathology research[5] and assessment of new therapies[6]. The purpose of this study was to investigate the sensitivity of ihMT in a EAE murine model. IhMT experiments were performed at different days after peptide injection and sensitivity for pathology was assessed by measurement of ihMT ratios, a potential surrogate measure of myelin content, in several brain structures.

Method:
Male C57BL/6J mice (age 8 weeks) were immunized by injection of MOG_{33-55} emulsified in complete Freund adjuvant and of *Bordetella pertussis* toxin. Brain MRI was performed at days 14, 34 and 71 after immunization, on a Bruker Avance 500 MHz/89 mm wide bore vertical imager (Bruker, Ettlingen, Germany). IhMT imaging was realized with a pulsed saturation preparation scheme[2,4], 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 MT images with ihMT=MT(+Δf) + MT(-Δf) – MT(+/-Δf) – MT(-/+Δf). MT(+Δf) corresponded to MT images obtained with single frequency offset saturation (all RF pulses applied at +Δf frequency offset) and MT(+/-Δf), to MT images obtained with dual frequency offset saturation (RF pulses applied at alternated +Δf and -Δf frequency offsets). Main parameters of the ihMT preparation were: pulse width=3ms, interpulse repetition time=3.3ms, frequency offsets $|\Delta f|$ =8kHz, saturation time τ=900ms and integrated squared B_1 (proportional to energy deposition, defined as $Etr=B_{1rms}x\tau=30uT^2s$). 60 NEX (acq. time 12 minutes) of each MT image were acquired to increase the SNR. IhMT experiment was repeated twice in order to acquire 2 slices, placed 1.7mm caudally and rostrally from Bregma. An additional unsaturated free water image (S_0) was acquired to derive quantitative ihMT and MT ratios as $ihMTR=ihMT/S_0$ and $MTR=1-MT(+\Delta f)/S_0$. Measurements (mean±standard deviation) were performed in ROIs selected in internal capsule (IC), corpus callosum (CC), cortex gray matter (cGM) and trigeminal nerves (TN).

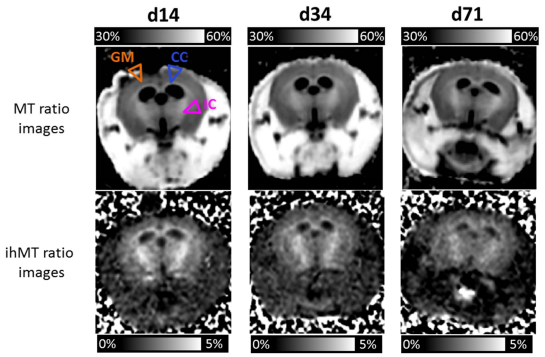

Fig 1 : axial MTR and ihMTR images showing different sentivity for myelinated structures over time.

Results and Discussion:
IhMTR and MTR images obtained at days 14, 34 and 71 after peptide injection are shown on Fig 1. Besides strong specificity for WM, decrease of ihMTR signal can also be clearly be seen in IC and CC between d14 and d71. In contrast, no significant change with time was noticed for MTR images. Quantitative IhMTR and MTR values, measured in IC (pink curves), CC (blue curves), cGM (orange curves) and TN (green curves) are reported on Fig 2a and 2b respectively. In highly myelinated brain structures, ihMT signal decreased from 4.3% to 3% for IC and from 3.3% to 2.7% for CC between d14 and d71. IhMTR values in low myelinated GM remained constant with time (~1.9%). Comparatively, MTR did not show any variation with time in IC (MTR~50%), CC (MTR~45%) and GM (MTR~42%). The observed invariance of MTR is in line with a previous study performed on the same EAE model, at day 13, 20 and 27 after peptide injection[6]. In TN though, pronounced signal changes were observed for both ihMTR and MTR, between d14 and d71: ratio values decreased from ~3.6% to ~1.9% for ihMTR (i.e. -89% of variation) and from ~47% to ~43% for MTR (i.e. -10% of variation). TN, as a structure not protected by the blood brain barrier, is prone to inflammation, and high sensitivity of MT for structural changes induced by inflammatory processes[5] may explain observed MTR values decrease. All combined, these result suggested that the observed ihMTR decrease was not due to increase in inflammation (constant MTR), but potentially ongoing demyelination processes.

Conclusion:
This study focused on the sensitivity of ihMT for pathology and the technique was applied on a mouse model of MS (EAE-MOG) at very high field (11.75 T). These results highlighted the complementarity of both ihMT and classical MT for providing information related to myelin content independently of inflammatory processes occurring in this model. Main limits of this preliminary study concern the size of the cohort as well as the absence of measurement during the early phase of inflammation (days<14). Future studies will thus imply ihMTR/MTR measurements on a bigger group of EAE-MOG model/control mice, at different time points. In parallel, histological measurements will be performed to validate ihMT as a technique specific to myelin able to provide longitudinal monitoring of demyelination/remyelination.

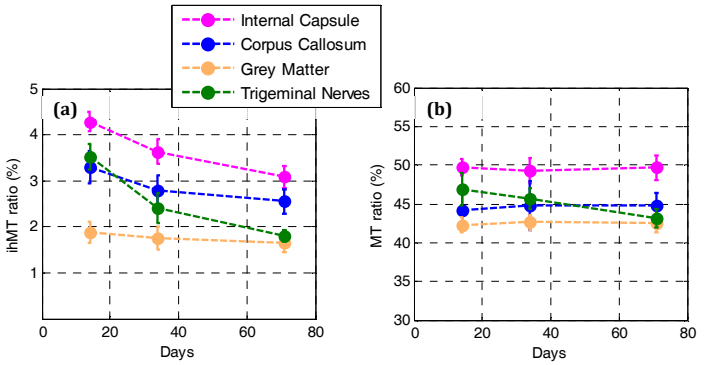

Fig 2 : ihMTR (a) and MTR (b) variations with time after peptide injection.

References: [1] Varma *et al*, Magn Reson Med (2014) PMID: 24604578, [2] Girard *et al*, Magn Reson Med (2014) PMID: 24962257 [3] Duhamel *et al*, Proc. ISMRM 2013;p2506 [4] Prevost *et al*, Proc. ISMRM 2014;p1498 [5] Serres *et al*, NMR in biomed (2009) [6] Aharoni *et al*, Experimental Neurology (2013)