Specificity of the Inhomogeneous Magnetization Transfer Approach to Myelinated Tissues

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Introduction: Magnetization transfer (MT) contrast has gained attention in the context of white matter disorders, such as multiple sclerosis[1]. However, MT is not a unique marker of myelin, and MT changes between healthy and diseased white matter (WM) tissue can be quite small. A technique called inhomogeneous magnetization transfer (IHMT[2-4]) imaging has been previously proposed as an alternative to MT. IHMT originates from more mobile macromolecules that give rise to inhomogeneously broadened lines, and can be isolated using alternating positive and negative off-resonance frequencies in the MT experiment. Although absolute quantified values of IHMT are small, they were found to be consistently higher in white matter (WM) than in any other tissue[5-7], making IHMT potentially sensitive to myelin. In this study, we investigate IHMT as a potentially specific marker of myelin by comparing IHMT and MT ratios in tissues and organs along the spine and in the abdomen.

Methods: Images were acquired in the spine and abdomen of five healthy volunteers using a 3.0 T scanner (GE Healthcare, Waukesha, WI). Inhomogeneous MT images were acquired by applying a pulsed saturation scheme for 500 ms, consisting of 35 mG (rms), 500 μs Hanning-shaped pulses applied every 1.5 ms with a +/- 7.0 kHz frequency offset to acquire four images in each set, as follows: positive frequency offset (A), alternating dual frequency offset (B), negative frequency offset (C), alternating dual frequency offset (D), which yields an IHMT component = (A+C)-(B+D). Following the saturation, a single slice was acquired using single-shot fast spin-echo (FSE) in the sagittal plane comprising the brainstem, and cervical and thoracic spine and spinal cord using a twelve-channel cervical-thoracic-lumbar RF coil, with the following imaging parameters: TR/TE = 2500/46 ms, FOV = 28 cm, phase FOV = 0.5, acquisition matrix 128 × 64, slice thickness = 10 mm, with 32 averages of each set and an additional eight averages of the unsaturated FSE image, for a total scan duration of six minutes. Next, the IHMT pulse sequence was used to acquire abdominal images using an eight-channel torso RF coil, and in a coronal plane comprising the kidneys, liver, and spleen, with the volunteers holding their breath during acquisitions. All parameters including those for the MT preparation remained the same, except the following: TR = 6000/36 ms, FOV = 40 cm, number of averages = 12, with 8 unsaturated images, for a total scan duration of about five minutes.

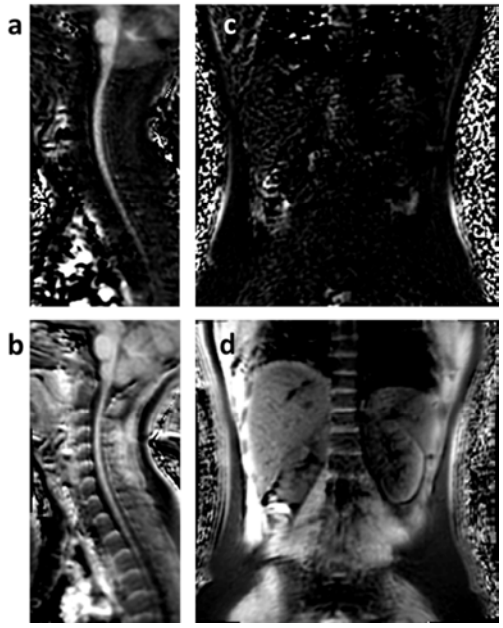

Figure 1 *illustrates the specificity of the IHMT approach to myelin, by comparing (a,c) IHMTR maps with (b,d) MTR maps in the (a,b) spine and (c,d) abdomen. IHMTR values in white matter are ~4.6%, and virtually zero in all other tissues not containing myelin.*

Tissue / Region	IHMTR (%)	MTR (%)
Cerebellar GM	1.7 ± 0.2	17.1 ± 1.5
Cerebellar WM	4.6 ± 0.3	23.7 ± 2.8
Spinal cord (C4-C5)	4.6 ± 0.5	20.9 ± 1.5
Vertebra (C4)	0.5 ± 0.4	8.3 ± 2.6
Intervertebral disk (C4-C5)	0.3 ± 0.3	27.9 ± 4.1
Kidney (cortex)	0.02 ± 0.4	10.2 ± 4.4
Liver	0.3 ± 0.3	16.8 ± 4.9
Spleen	-0.2 ± 0.3	6.3 ± 2.0
Psoas muscle	0.1 ± 0.6	15.1 ± 5.9

Table 1 *compares IHMTR and MTR values in various tissues.*

Inhomogeneous MT ratio (IHMTR) maps were calculated by normalizing the IHMT images by the unsaturated FSE images. For comparison, MT ratio (MTR) maps were also calculated using image 'A' as the saturated image. A region of interest analysis was used to compare the IHMTR against the MTR, in cerebellar gray and white matter and the C4-C5 region of the spinal cord, vertebrae, and intervertebral disks on the spine images and in the cortex of the kidney, liver, spleen, and psoas muscle on the abdominal MR images.

Results: Figure 1 shows (a,c) IHMTR and (b,d) MTR maps in the (a,b) spine and (c,d) abdomen. IHMTR ratios in Table 1 are clearly specific to myelin, with values of 4.6% in white matter and 1.7% in grey matter which has far less myelination than white matter. None of the other tissues shows a significant IHMTR. In contrast, MTR values range from 6.3% in spleen to 27.9% in intervertebral disk, with values of 23.7% in white matter, and are clearly not specific to myelinated tissues.

Discussion and Conclusions: Unlike standard MT, the inhomogeneous MT component was shown to be sensitive and specific to white matter, most likely myelin. This is thought to be because the lamellar structures in myelin are composed of long lipid chains that manifest as inhomogeneously broadened lineshapes (in NMR spectra)[8] that are detected in the IHMT approach. Though the signal from the inhomogeneously broadened lines is smaller than from the full MT effect, its increased specificity may merit its use in studies of myelination and myelinated tissues.

References: (1) Filippi *et al*., *J Neuroimg*, 14:p303, 2004 (2) Alsop *et al.*, *ISMRM* 2004, p2324 (3) Alsop *et al.*, *ISMRM* 2005, p2224 (4) Alsop *et al.*, *ISMRM* 2007, p2188 (5) Varma *et al.*, *ISMRM* 2013, p4526 (6) Girard *et al.*, *ISMRM* 2013, p1855 (7) Rangwala *et al.*, *ISMRM* 2013, p350 (8) Seiter *et al.*, *Jnl. Am. Chem. Soc.*, 95:p7541, 1973.