Quantitative Magnetization Transfer Imaging at 7 Tesla: Application in Multiple Sclerosis Patients and Validation in Postmortem Brain
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Target Audience: 1) imaging scientists interested in quantitative imaging at high field and 2) the White Matter Study Group of the ISMRM

Purpose: Quantitative magnetization transfer (qMT) imaging has been previously used to assay myelin content in white matter [1–4]. Although promising, qMT imaging is often limited by long scan times. To decrease scan times, we recently [5] developed a selective inversion recovery (SIR) qMT protocol that exploits the increased signal-to-noise ratio (SNR) available at 7.0 T. Similar to previous work at lower fields [1–4], results from this high-field study suggest that macromolecular to free pool-size-ratio (PSR) is related to myelin content in healthy controls. The goals of the study herein are: 1) to establish the relationship between PSR and pathological changes in relapsing-remitting multiple sclerosis (RRMS) patients and 2) to validate the SIR technique by comparing qMT parameter maps in postmortem RRMS brains to histological measurements of myelin content.

Methods: Postmortem Sample Processing: Three samples were donated from the Rocky Mountain MS brain bank (Englewood, Colorado). Samples were fixed (10% formalin), sectioned into 10-mm coronal slices, placed in an MR-compatible holder filled with fixative, and MRI-ed in five healthy volunteers (23–38 y.o.), six RRMS patients (33–65 y.o.), and three postmortem brains using a 7.0-T Philips MR scanner with a 32-channel head receive coil. The pulse sequence [5] employed a B1+-insensitive inversion pulse, a variable duration inversion recovery period to sample the MT-related biexponential recovery, and a turbo field echo (TFE) readout. Data were acquired in postmortem brains using: inversion times = 6–2000 ms (16 values), pre-delay time = 1.0 s, TFE pulse interval/TE/flip angle = 5.6 ms/2.6 ms/15°, echoes per shot = 71, resolution = 0.7x0.7x0.7 mm³, and field-of-view (FOV) = 150x150x28 mm³. A similar, lower resolution (2x2x3 mm³, FOV = 212x212x75 mm³), protocol was used for in vivo studies (see [5] for details). Data Analysis: SIR-TFE data were fit to a biexponential model of the MT effect and the resulting rate constants and amplitudes were related to qMT parameters [6], including: PSR, the MT rate from the free to macromolecular pool (kmf), and the Rf of the free pool (Rf). For the in vivo studies, normal-appearing white matter (NAWM) was segmented by thresholding the Rf maps and a histogram analysis was performed. For each histogram, the parameter value at the maximum histogram value (Pm) and the root-mean-squared deviation about Pm (RMSD) were tabulated. For the postmortem studies, ROIs were defined in lesions, NAWM, and normal-appearing gray matter (NAGM) in the qMT parameter maps and corresponding histology slides. Pearson’s correlation coefficient was tabulated to assess the relationship between qMT parameters and the optical density (OD) of the LFB sections.

Results and Discussion: In vivo studies: Fig. 1 shows sample parameter maps from a healthy volunteer (top tow) and RRMS patient (middle row) along with corresponding histograms from NAWM (bottom row). Focal decreases in PSR and Rf were observed in lesions (black arrow). In addition, shifted and broadened parameter histograms were observed for PSR (healthy: Pm = 17±1%, RMSD = 2±1%; RRMS: Pm = 15±2%, RMSD = 3±1%) and Rf (healthy: Pm = 65±0.03 s⁻¹, RMSD = 0.07±0.02 s⁻¹; RRMS: Pm = 60±0.08 s⁻¹, RMSD = 0.08±0.04 s⁻¹) throughout NAWM. Consistent with a previous study of spinal WM [7], similar kmf values were observed in healthy and RRMS brains. While these results suggest that PSR and Rf are sensitive to changes in myelin content, other pathological features (e.g., inflammation, axonal loss) may also be contributing to the observed differences between the healthy and RRMS cohorts. The postmortem study was designed to assess the relationship between myelin content and the SIR-derived parameters. Postmortem studies: Fig. 2 (top row) shows a sample LFB section and corresponding qMT parameter maps. Similar to the in vivo results, focal decreases were observed in PSR and Rf within lesions (black arrows) in the postmortem brains. From the correlation analysis (bottom row), a significant correlation between PSR and myelin content was detected. The increase in PSR relative to the in vivo studies, which is likely due to cross-linking from fixation. Rf correlated more strongly with myelin content than PSR; however, this stronger correlation is likely driven by the lower uncertainty in the Rf estimate [6] and may be nonlinear (see dashed gray line) due to the sensitivity of Rf to other pathological features (e.g., inflammation). Consistent with the in vivo findings, a weak correlation was detected between kmf and myelin content (r² = 0.24, p = 0.04). Together, these results suggest that PSR (and potentially Rf) values can be used as a marker for myelin content in RRMS patients at 7.0 T.


Fig. 1. Parameter maps from a control (top) and RRMS patient (middle) and mean NAWM histograms across each cohort (bottom).

Fig. 2. Postmortem histology and SIR parameter maps from a representative brain (top) and scatterplot of PSR and Rf versus the LFB-derived OD values (bottom).