Reproducibility of quantitative magnetization transfer imaging parameters

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Introduction: Magnetization transfer MR imaging (MTI) is a proven tool in the study of cerebral tissue, especially in characterizing white matter, and has been demonstrated by histopathology to correlate strongly with demyelination in patients with multiple sclerosis [1]. Techniques have been developed to enable quantitative imaging experiments based on the binary spin bath model of tissue [2,3,4], and provide estimates of model parameters such as the relative size of the restricted proton pool (F), the magnetization exchange constant (k_f), as well as most of the relaxation parameters of both model compartments (R_{1f}, T_{2f}, T_{2r}). To utilize quantitative methods in longitudinal studies, it is necessary to assess their reproducibility. The goal of this study was to evaluate the variability in parameter estimates obtained using our quantitative magnetization transfer imaging technique (QMTI) [2].

Methods: Magnetization transfer and relaxometry data were acquired in a single oblique 7-mm section of four healthy subjects (gender/age/number of exams: M/29/2, M/40/6, F/34/2, F/26/2) at multiple time points over a period of two years, using the imaging protocol described in [2,5]. Inter-scan periods ranged from 2 months to 2 years, and all data were acquired on a 1.5 T Sonata (Siemens Medical Systems, Erlangen, Germany). Care was taken to reproduce the initial slice position for each subject as closely as possible at each exam. Different slice positions were used for each subject due to requirements of the larger studies in which they were participating. Data were processed to yield maps of the final set of model parameters, including corrections for static and RF transmit field inhomogeneities. Seventeen (17) white and grey matter regions-of-interest (ROIs) were manually identified on the high-resolution scans of each subject and re-sampled to the lower resolution of the quantitative scans. Image voxels with obvious partial voluming when registered to the high-resolution scans, or where the fit chi-squared value exceeded 8 standard deviations (to separate misfit due to measurement noise from failure of the optimization procedure), were excluded from the regions-of-interest for the analysis.

Results: No obvious left-right differences were observed between structure pairs, reflecting previous observations [5], and so the analysis was performed after combining left and right homologous ROIs. Ten final ROIs were retained, and are listed in Table 1. Parameters were normally distributed within each ROI, and so the mean and standard deviation for each region-of-interest were used for this analysis. Intra-subject reproducibility was evaluated by computing the coefficient of variation (CoV) of each parameter for each region-of-interest in each subject across scans. Since the variability of the final fitting parameters depends in part on the variability of the input normalized MT-weighted (MTw) data, this was also evaluated. The mean variability of the MTw data (across all weightings) for this study ranged from 0.4 to 1.0% depending on the subject and region-of-interest, with maximum variability occurring for weightings obtained using near-resonance saturation pulses (range 4.3-16.5%). The resulting CoV values for each parameter were then averaged across subjects for each region-of-interest, and are presented along with the range of observed values in Table 1. Since the slice position was different across subjects, the available ROIs were different for each individual, thus precluding the analysis of inter-subject and inter-region variability. However, comparison to previously reported data [5] indicated that the intra-subject variability seen in this study is generally inferior to observed inter-subject differences, even over long inter-scan periods.

Discussion: We have demonstrated that serial quantitative MT-MRI experiments can be performed reliably with an average variability of 6% for the relative size of the restricted pool F, 10% for the exchange constant k_f, 2.4% on the T_2 of the restricted pool (T_{2r}), and 2.1% on the free pool relaxation constant R_{1f}. The free pool T_{2f} is slightly more difficult to constrain (variability of 12.9%), reflecting the greater variability in the MTw data near resonance; however, this has a negligible direct impact on the estimates of other parameters. The variability of the parameter estimates combines the effects of biological variations, noise and drift in the data acquisition, slice-positioning by the radiology technician, and fitting error. The quality of the resulting model fit is weakly dependent on the quality of the acquired MTw data: increased variability in the MTw data generally leads to greater variability of the QMTI parameter estimates, in particular for T_{2f} and k_f. Improvements may result from higher-resolution exams, by reducing the partial volume effect, but these findings are near the currently attainable limit given the careful selection of voxels to eliminate such effects. The findings from this study establish the feasibility of using quantitative magnetization transfer MRI techniques for the monitoring of changes in patients affected by degenerative white matter diseases, and provide data on which to base the statistical power of longitudinal studies.

Table 1. Coefficients-of-variation (CoV) of the MT-weighted data and QMTI parameter estimates, by region-of-interest (the number of subjects is indicated in parentheses). The mean CoV of the MTw data is computed across weightings for each region, then averaged across subjects where applicable.

	MTw data		<CoV> of QMTI parameter estimates				
Region-of –interest	**<CoV>**	**max(CoV)**	**F**	**k_f**	**R_{1f}**	**T_{2f}**	**T_{2r}**
Centrum semiovale – anterior (n = 1)	**1.0 %**	**16.5 %**	4.3 %	10.9 %	4.3 %	16.4 %	3.1 %
middle (n = 1)	**0.4 %**	**4.9 %**	9.1 %	13.2 %	0.9 %	11.5 %	3.3 %
posterior (n = 3)	**0.4 %**	**10.8 %**	5.2 %	9.8 %	1.7 %	12.6 %	2.3%
Minor forceps (n = 3)	**0.5 %**	**10.6 %**	4.7 %	7.2 %	0.6 %	9.0 %	2.3 %
Major forceps (n = 1)	**0.6 %**	**4.3 %**	5.6 %	11.3 %	3.3 %	9.8 %	1.5 %
Corpus callosum – genu (n = 1)	**0.8 %**	**10.5 %**	7.9 %	17.0 %	2.8 %	17.2 %	3.0 %
body (n = 2)	**0.6 %**	**9.4 %**	6.9 %	5.8 %	1.3 %	5.6 %	2.6 %
splenium (n =1)	**0.6 %**	**5.1 %**	4.5 %	12.2 %	1.6 %	15.9 %	1.2 %
Corona radiata (n = 1)	**0.4 %**	**4.6 %**	2.2 %	7.1 %	2.7 %	10.4 %	2.7 %
Caudate nuclei (n = 1)	**0.9 %**	**9.0 %**	13.7 %	21.2 %	5.6 %	37.2 %	2.7 %
<CoV>			**6.0 %**	**10.3 %**	**2.1 %**	**12.9 %**	**2.4 %**
Range over all subjects	**0.4 – 1.0 %**	**4.3 – 16.5 %**	**2,2-13.7 %**	**4.1-21 %**	**0.2-5.6 %**	**0.3-37.2 %**	**0.9-13.8 %**
Inter-subject <CoV> based on [5]			**9 %**	**12 %**	**5 %**	(n/a)	**4.3 %**
Range			**8-12 %**	**8-18 %**	**3-6 %**	(n/a)	**2-7%**

References

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