論文の内容の要旨

論文題目　Basic Study of Synthetic MRI and Its Application to Multiple Sclerosis
(Synthetic MRI の基礎的検討と多発性硬化症への適用)

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In clinical practice, T1-weighted, T2-weighted, fluid-attenuated inversion recovery, and other contrast-weighted MRI images are assessed on the basis of relative signal differences. The signal intensity depends on sequence parameters and scanner settings, but also on B0 and B1 inhomogeneity, coil sensitivity profiles and radio frequency amplification settings, making quantitative comparisons difficult. Tissue relaxometry is a more direct approach to obtaining scanner-independent values. Absolute quantification of tissue properties by relaxometry has been reported in research settings for characterization of disease, assessment of disease activity, and monitoring of treatment effect. A number of methods have been proposed for simultaneous relaxometry of T1 and T2, but due to the additional scanning time required, these methods had not been widely introduced into clinical practice. Recently, QRAPMASTER (quantification of relaxation times and proton density by multiecho acquisition of a saturation-recovery using turbo spin-echo readout) pulse sequence for rapid simultaneous measurement of T1 and T2 relaxation times (and their inverses R1 and R2 relaxation rates) and proton density (PD), with correction of B1 field inhomogeneity, was proposed for full head coverage within approximately 6 minutes. These quantitative values allow post-acquisition generation of any contrast-weighted image via synthetic MRI, obviating the need for additional conventional T1-weighted and T2-weighted imaging required in routine clinical settings. The acquired maps are inherently aligned, thus avoiding potential errors due to image coregistration for multi-parametric quantification of a certain area. Myelin estimation can also be performed based on the acquired T1, T2, and PD values. The entire technique is referred to as synthetic MRI, or SyMRI. Herein, we conducted three consecutive studies to evaluate the quantitative values acquired by the QRAPMASTER pulse sequence for synthetic magnetic resonance imaging (MRI) and its application to multiple sclerosis (MS).

According to the Quantitative Imaging Biomarkers Alliance of the Radiological Society of North America, three metrology criteria are critical to the performance of a quantitative imaging biomarker: accuracy, repeatability, and reproducibility. Previous studies evaluated T1, T2, and PD values acquired with the QRAPMASTER sequence on a 1.5T scanner, by assessing accuracy, repeatability, and reproducibility using different head coils. However, to our knowledge, no study has compared quantitative values acquired with the MDME sequence on different scanners. The aim of the first study was to evaluate the linearity, bias, intrascanner repeatability, and interscanner reproducibility of quantitative values derived from the QRAPMASTER sequence for rapid simultaneous relaxometry. The NIST/ISMRM (National Institute of Standards and Technology/International Society for Magnetic Resonance in Medicine) phantom, containing spheres with standardized T1 and T2 relaxation times and proton density (PD), and 10 healthy volunteers,

were scanned 10 times on different days and 2 times during the same session, using the QRAPMASTER sequence, on three 3 T scanners from different vendors. For healthy volunteers, brain volumetry and myelin estimation were performed based on the measured T1, T2, and PD. The measured phantom values were compared with reference values; volunteer values were compared with their averages across 3 scanners. The linearity of both phantom and volunteer measurements in T1, T2, and PD values was very strong (R^2 = 0.973–1.000, 0.979–1.000, and 0.982–0.999, respectively) The highest intrascanner coefficients of variation (CVs) for T1, T2, and PD were 2.07%, 7.60%, and 12.86% for phantom data, and 1.33%, 0.89%, and 0.77% for volunteer data, respectively. The highest interscanner CVs of T1, T2, and PD were 10.86%, 15.27%, and 9.95% for phantom data, and 3.15%, 5.76%, and 3.21% for volunteer data, respectively. Variation of T1 and T2 tended to be larger at higher values outside the range of those typically observed in brain tissue. The highest intrascanner and interscanner CVs for brain tissue volumetry were 2.50% and 5.74%, respectively, for cerebrospinal fluid. In conclusion, quantitative values derived from the QRAPMASTER sequence are overall robust for brain relaxometry and volumetry on 3 T scanners from different ven- dors. Caution is warranted when applying MDME sequence on anatomies with relaxometry values outside the range of those typically observed in brain tissue.

The aim of the second study was to validate the synthetic myelin imaging by comparing it with other myelin imaging methods. Magnetization transfer (MT) imaging has been widely used for estimating myelin content in the brain. Recently, two other approaches, namely SyMRI and the ratio of T1-weighted to T2-weighted images (T_1w/T_2w ratio), were also proposed as methods for measuring myelin. SyMRI and MT imaging have been reported to correlate well with actual myelin by histology. However, for T_1w/T_2w ratio, such evidence is limited. Investigation of correlation among different myelin imaging methods is scarce. Specifically, no study has examined the correlation of SyMRI as a myelin imaging tool with other methods. In 20 healthy adults, we examined the correlation between these three methods, using MT saturation index (MTsat) for MT imaging. After calibration, white matter (WM) to gray matter (GM) contrast was the highest for SyMRI among these three metrics. Even though SyMRI and MTsat showed strong correlation in the WM (r = 0.72), only weak correlation was found between T1w/T2w and SyMRI (r = 0.45) or MTsat (r = 0.38) (correlation coefficients significantly different from each other, with *P* values < 0.001). In subcortical and cortical GM, these measurements showed moderate to strong correlations to each other (r = 0.54 to 0.78). In conclusion, the high correlation between SyMRI and MTsat indicates that both methods are similarly suited to measure myelin in the WM, whereas T1w/T2w ratio may be less optimal.

The purpose of the third study was to evaluate SyMRI myelin imaging model that assesses myelin and edema for characterizing plaques, periplaque white matter, and normal-appearing white matter in patients with MS. We examined 3T SyMRI data from 21 patients with MS. The myelin partial volume, excess parenchymal water partial volume, the inverse of T1 and transverse T2 relaxation times (R1, R2), and proton density were compared among plaques, periplaque white matter, and normal-appearing white

matter. All metrics differed significantly across the 3 groups ($P < 0.001$). Those in plaques differed most from those in normal-appearing white matter. The percentage changes of the metrics in plaques and periplaque white matter relative to normal-appearing white matter were significantly more different from zero for myelin volume fraction (mean, -61.59 ± 20.28% [plaque relative to normal-appearing white matter], and mean, -10.51 ± 11.41% [periplaque white matter relative to normal-appearing white matter]), and excess parenchymal water volume fraction (13.82 × 10^3 ± 49.47 × 10^3% and 51.33 × 10^2 ± 155.31 × 10^2%) than for R1 (-35.23 × 13.93% and -6.08 ± 8.66%), R2 (-21.06 ± 11.39% and -4.79 ± 6.79%), and PD (23.37 ± 10.30% and 3.37 ± 4.24%). SyMRI captures white matter damage in MS. Myelin volume fraction and excess parenchymal water volume fraction are more sensitive to the MS disease process than R1, R2, and PD. MVF and EPWVF could be useful estimators of disease burden in patients with MS.

In summary, I conclude that QRAPMASTER can perform quantitative measurement of the brain with high accuracy and precision in a short acquisition time. The technique may be clinically useful in the assessment of brain disorders including MS.