Cartilage MR T1ρ And T2 Quantifications: Longitudinal Reproducibility And Variations Using Different Coils And Scanners At Single And Multi-sites

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Introduction: Quantitative magnetic resonance imaging (MRI) of articular cartilage matrix composition, including T1ρ and T2 mapping, are promising techniques that have potential as early markers of cartilage degeneration; these methods however also present significant challenges with a high threshold for quantification accuracy to make measurements in a thin curved structure. Currently, applications of cartilage T1ρ and T2 imaging in multicenter clinical trials are very limited. One impeding factor is the lack of documentation of potential variations of T1ρ and T2 introduced by different scanners, coils and sites. Further, previous studies on reproducibility of T1ρ and T2 quantification were primarily limited to short-term measurements, except for a recent report on 8-year T2 quantification as part of the Osteoarthritis Initiative (OAI) study quality control procedure (1). Currently, a multi-center feasibility study applying T1ρ and T2 imaging in knees after acute ACL injury, which is a high risk-factor for post-traumatic OA, is being performed among three sites. In this report, we evaluate the longitudinal reproducibility of T1ρ and T2, and the variation of T1ρ and T2 by using different scanners and coils at one site, and the reproducibility and cross-validation of T1ρ and T2 among the three sites.

Methods: Figure 1 illustrates the overall study design including the single-site and multi-site evaluations. 3T GE HDx, MR750 and MR750 Wide Bore scanners were used for the single-site study and only MR750 scanners were used for the multi-site study. Custom phantom sets with agarose concentrations varying from 2%-4% were scanned at isocenter, left 70mm and right 70mm positions. A 3D sequence that combines T1ρ and T2 quantification in one acquisition was applied (2). The same phantom and in vivo imaging protocol were applied at all three sites with the same parameters (FOV = 14 cm, matrix size = 256 x 128, slice thickness = 4 mm, time of spin-lock (TSL) = 0/10/40/80 ms, frequency of spin-lock = 500 Hz; magnetization preparation TE = 0/12.8/25.7/51.4 ms). High-resolution 3D FSE images (CUBE, FOV = 14 cm, matrix size = 384 x 384 slice thickness = 1mm) were registered to T1ρ and T2 maps and cartilage was segmented semi-automatically using in-house developed software (3) on the registered CUBE images. T1ρ and T2 relaxation times were calculated in phantoms and in anatomically defined compartments in vivo. All data analysis was performed at one site. The reproducibility and differences were evaluated using Bland-Altman method, and calculation of root-mean-square coefficients of variation (RMS-CV, %), absolute difference (in ms) and intra-class correlation (ICC).

Results: Single-Site Study Long-term reproducibility (up to 30 months): The RMS-CV was 1.8%, 2.0% and 2.1% for T1ρ and 2.3%, 2.9% and 2.8% for T2 for HDx Long Bore, MR750 and MR750 Wide Bore
respectively. Variations using different model of scanners: T1ρ and T2 values measured with the MR750 Wide Bore were significantly lower compared to using the HDx Long Bore. In phantoms: the mean CV was 2.7% and 1.0% and the mean absolute difference was 1.7 ± 1.3 ms and 0.4 ± 0.4 ms for T1ρ and T2 respectively; In healthy volunteers (n=10), the absolute difference was 4.5 ± 2.4 ms for T1ρ and 2.2 ± 1.6 ms for T2. Variations using different coils: Using the MR750 Wide Bore, T1ρ and T2 values were significantly higher using the 16-channel coil than those using the 8-channel coil in healthy volunteers (n=5). The absolute difference was 3.5 ± 2.1 ms for T1ρ and 1.5 ± 1.4 ms for T2. Multi-Site Study Reproducibility in phantoms (up to 8 months): The RMS-CV was 1.8%, 2.3% and 1.5% for T1ρ and 2.1%, 3.8% and 1.8% for T2 for site 1, 2 and 3 respectively. In vivo scan-rescan reproducibility: Across all three sites (n=16), the scan-rescan RMS-CV was 3.1% and 4.0% and the mean absolute difference was 1.9 ms and 1.8 ms for T1ρ and T2, respectively, Figure 2. The RMS-CV in each compartment ranged from 2.3% - 3.9% for T1ρ, and ranged 3.2% - 5.3% for T2. Cross-validation among three sites: Phantom T1ρ and T2 values were significantly different among three sites but highly correlated (ICC > 0.99). The CV was 2.1% and 3.2% between site 1 and 2, and was 4.3% and 3.6% between site 1 and 3 for T1ρ and T2 respectively. No significance difference was found in T1ρ and T2 values in the traveling controls (n=2) who were scanned at all three sites. The RMS-CV was 4.7% and 4.8% with absolute difference as 1.3 ms and 1.0 ms for T1ρ and T2, respectively.

**Discussion:** This is the first report on longitudinal reproducibility of T1ρ quantification in phantoms, and T1ρ and T2 quantification on the same phantoms and volunteers across multiple sites. Single-site study The CV of repeated T1ρ and T2 measurements up to 30 months were all less than 3%, indicating excellent longitudinal reproducibility. No notable system drift was observed. The differences of system hardware (e.g. peak gradient amplitude, gradient slew rate, and bore size) among the three scanners used in the single-site study could produce different pulse widths and minimal TRs/TEs resulting in the observed differences of T1ρ and T2 values among the scanners. In addition, different RF coil transmit uniformity and load, flip angle accuracy, and signal-to-noise ratio can also introduce variations in the relaxation time quantification (4). Multi-site study This study was designed to utilize the same model of MR scanner and RF coil, and the same sequence to minimize potential inter-site differences. The overall scan/re-scans reproducibility CV was comparable to single site CVs and was better compared to previously reported multi-site studies (5), which can be attributed to the stringent study design requiring the same hardware and scanning software at all sites and the centralized data analysis with stringent quality control. Although significant differences were observed in phantom T1ρ and T2 values, the values between sites were highly correlated (ICC > 0.99), suggesting the bias might be readily correctable during data analysis. No significant differences of T1ρ and T2 values were observed in cartilage of traveling controls, suggesting that the variation introduced by different sites (as observed in phantoms) were smaller in magnitude compared to scan/re-scan measurement errors. In conclusion, the results from this study suggest that with careful quality control and cross-calibration, quantitative MRI can be readily applied in multi-site studies and clinical trials for evaluating cartilage degeneration. Future studies will expand the multi-site study to include scanners from multiple manufacturers.

**Significance:** Quantitative MRI of cartilage can detect early and subtle changes during cartilage degeneration, which is critical for allowing early intervention, monitoring treatments and allowing prevention strategies for osteoarthritis. Understanding and documenting longitudinal reproducibility
and cross-validation between sites of cartilage MR T1ρ and T2 are critical for setting up multi-center longitudinal studies and clinical trials using these advanced techniques.

**Figure 1.** Flow chart of the overall study design. The single-site study was designed to evaluate: 1) long-term reproducibility of \( T_{1\rho} \) and \( T_2 \) using three GE 3T scanners (GE HDx Long Bore; GE MR750; GE MR750 Wide Bore) using 8-channel transmit/receive knee coils by scanning agarose phantoms monthly for up to 30 months; 2) the variation of \( T_{1\rho} \) and \( T_2 \) using two scanners (GE HDx Long Bore vs GE MR750 Wide Bore) with the same 8-channel knee coil; 3) the variation of \( T_{1\rho} \) and \( T_2 \) quantification at one scanner (MR750 Wide Bore) using two coils (8-channel knee coil vs. 16-channel receive only flex coil). All the data were collected between 2011 September to 2014 July. The multi-site study was designed to evaluate: 1) reproducibility of \( T_{1\rho} \) and \( T_2 \) quantification in phantoms scanned monthly at each site; 2) scan-re-scan reproducibility of \( T_{1\rho} \) and \( T_2 \) quantification in healthy controls at each site; 3) variation of \( T_{1\rho} \) and \( T_2 \) quantification in same phantoms and in same volunteers across three sites. All three sites used GE MR750 scanners with an 8-channel knee coil. All data were collected between 2013 November and 2014 July.
Figure 2. Scan-rescan reproducibility of $T_{1p}$ and $T_2$ values in healthy controls in a three site study. LFC: lateral femoral condyle; LT: lateral tibia; MFC: medial femoral condyle; MT: medial tibia; PAT: patella; TRO: trochlea.

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