

## T2 values of articular cartilage in clinically relevant subregions of the asymptomatic knee

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### Abstract

**Purpose** In order for T2 mapping to become more clinically applicable, reproducible subregions and standardized T2 parameters must be defined. This study sought to: (1) define clinically relevant subregions of knee cartilage using bone landmarks identifiable on both MR images and during arthroscopy and (2) determine healthy T2 values and T2 texture parameters within these subregions.

**Methods** Twenty-five asymptomatic volunteers (age 18–35) were evaluated with a sagittal T2 mapping sequence. Manual segmentation was performed by three raters, and cartilage was divided into twenty-one subregions modified from the International Cartilage Repair Society Articular Cartilage Mapping System. Mean T2 values and texture parameters (entropy, variance, contrast, homogeneity) were recorded for each subregion, and inter-rater and intra-rater reliability was assessed.

**Results** The central regions of the condyles had significantly higher T2 values than the posterior regions ( $P < 0.05$ ) and higher variance than the posterior region on the medial side ( $P < 0.001$ ). The central trochlea had significantly greater T2 values than the anterior and posterior condyles. The central lateral plateau had lower T2 values, lower variance, higher homogeneity, and lower contrast

than nearly all subregions in the tibia. The central patellar regions had higher entropy than the superior and inferior regions (each  $P \leq 0.001$ ). Repeatability was good to excellent for all subregions.

**Conclusion** Significant differences in mean T2 values and texture parameters were found between subregions in this carefully selected asymptomatic population, which suggest that there is normal variation of T2 values within the knee joint. The clinically relevant subregions were found to be robust as demonstrated by the overall high repeatability.

**Keywords** T2 mapping · Quantitative MRI · Knee · Texture analysis · Cartilage

### Introduction

Osteoarthritis (OA) is the most common type of arthritis and is the leading cause of disability among adults [1]. The noninvasive quantification of structural and biochemical properties related to the onset and progression of OA is critical for studies of this condition. Early detection of OA may make it a possibility to implement treatment strategies to slow or stop progression of the disease. Quantitative MRI cartilage mapping has demonstrated potential for detecting the early biochemical changes, which include a decrease in proteoglycans, a disruption of the cartilage matrix, and an influx of chondrocytes and water as a response to the area of damage, within cartilage with the ability to detect damage not visualized on conventional MRI [9, 26]. T2 mapping is the most commonly used noninvasive mapping technique as it is widely available, less time-consuming than most techniques, and has been reported to be sensitive to collagen matrix organization and water content of cartilage [11, 23, 37–40].

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Researchers have reported T2 mapping values of the knee in healthy populations including reporting global values, values from the tibiofemoral regions, and larger subregions or the entire cartilage plate [25, 35, 41]. However, the specific values associated with healthy cartilage are variable within the literature, and thus, the reproducibility among reports is uncertain. Moreover, the definition of “healthy” cartilage and the subregions used for analysis of T2 cartilage are inconstant across centres [18, 26, 41]. The International Cartilage Repair Society (ICRS) has developed a standardized method of evaluating cartilage damage which focuses on the lesion depth and the area of damage [4]. To aid in the arthroscopic assessment, the ICRS has described an articular cartilage mapping system which divides the knee into sections, allowing for a method of describing lesion location. A modified version of these regions may be appropriate to describe and detect small regions of cartilage variation in T2 mapping, because a set of comprehensive and standardized subregions would allow for the long-term assessment of cartilage health following treatment and allow for comparisons to be made across multiple institutions.

While mean T2 values are typically reported, important information may also be imbedded in the grey values of the MR image. Grey values in an image carry intensity information which is expressed as a range between black and white. Using information from grey values, the spatial pattern of T2 values (known as matrix-based texture analysis) has also been analysed and reported to correlate with varying stages of OA [6, 16, 20]. Texture analysis parameters (such as entropy, contrast, variance, and homogeneity) characterize the underlying structure of a given tissue present in an image and may provide a more comprehensive understanding of the cartilage structure than solely mean T2 values.

The purpose of this study was to define clinically relevant subregions of knee cartilage based on the ICRS articular cartilage mapping system using bone landmarks identifiable in both MRI and arthroscopy and to determine standardized, asymptomatic T2 parameter values (T2 values and texture analysis) for these subregions. It was hypothesized that T2 parameters would significantly differ between the proposed subregions based on the ICRS articular cartilage mapping system within the patellar, femoral, and tibial cartilage, and the proposed subregions would have excellent inter-rater and intra-rater repeatability among three raters with varying medical backgrounds.

## Materials and methods

Twenty-five asymptomatic volunteers (age 18–35) were enrolled. Volunteers were deemed asymptomatic by a

self-administered subjective scoring form (pain/swelling/stiffness visual analogue score), an objective clinical examination performed by a sports medicine orthopaedic surgeon, and by morphological MRI examination by a musculoskeletal radiologist. Clinical examination included evaluation of limb alignment, pain/tenderness, and the following tests: Lachman test, anterior, anterolateral, posterior, and posterolateral drawer, pivot, and reverse pivot shift test, and evaluation of the medial and lateral joint opening. Exclusion criteria included symptoms (e.g. pain, stiffness, and swelling exceeding mild levels) in the knee and/or hip of the imaged side, prior injury or surgery in the knee and hip, history of inflammatory arthritis or infection within the joint of interest, and evidence of cartilage lesions, meniscal pathology, or bone marrow signal changes from a conventional morphological MRI examination using a semi-quantitative modified whole-organ magnetic resonance imaging score (WORMS).

## Image acquisition

Magnetic resonance imaging was performed with a Siemens Magnetom Verio 3.0 T scanner (Siemens Medical Solutions, Erlangen, Germany) with a gradient strength of 40 mT/m, using a 15-channel multi-element phased-array knee coil (Quality Electrodynamics, LLC, Mayfield Village, OH, USA). The time delay between lying down for the MR session and the beginning of the first sequence was limited to <5 min.

The scanning protocol consisted of: (1) a 3D fat-suppressed Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (FS SPACE) scan, (2) a multi-echo spin-echo T2 mapping scan in the sagittal plane (MESE T2 Map Sag), (3) a proton density turbo spin-echo scan in the coronal plane (PD with TSE Cor), and (4) a T2-weighted turbo spin-echo scan in the axial plane (T2w TSE Ax). The SPACE scan was reformatted in all three planes (Table 1). T2 mapping was performed at the end of the examination following morphological scans, approximately 16 min after entering the scanner, because it has been suggested that the cartilage should be unloaded prior to obtaining T2 values [2]. It was theorized that 16 min would be an appropriate time to unload the subject because the length of the imaging session must be kept relatively short for patient comfort, the avoidance of movement artefacts, and to allow for the entire examination to fit into a typical workflow timeslot to be clinically applicable.

## Data analysis

### *MRI scoring*

To investigate pathology within the joint, MR images were graded using a reduced version of the whole-organ

**Table 1** Parameters of the imaging sequences used in the study

Sequence	T2 map sag	PD-TSE SPACE sag	T2w-TSE ax	T2w-PD-TSE cor
Repetition time (ms)	2,570	1,200	5,320	2,770
Echo time (ms)	13.8–96.6	45	100	33
Field of view (mm)	140	150	110	110
Matrix	256 × 256	256 × 256	256 × 192	320 × 256
Voxel size (mm)	0.5 × 0.5 × 2.0	0.6 × 0.6 × 0.7	0.6 × 0.4 × 3.0	0.4 × 0.3 × 3.0
Slice thickness (mm)	2	0.7	3	3
Interslice gap (mm)	1	0	0	0
Number of slices	25	176	35	33
Echo trains/slice	–	–	6	11
Turbo factor	–	84	20	14
Examination time	6:53	4:46	2:20	2:09

MR parameters for quantitative and morphological imaging

*Sag* sagittal, *PD* proton density, *TSE* turbo spin-echo, *SPACE* single slab 3D TSE sequence (sampling perfection with application optimized contrasts using different flip angle evolution), *Ax* axial, *Cor* coronal

magnetic resonance scoring system (WORMS) [20]. The WORMS evaluation consists of a semi-quantitative score for 14 features in the knee [28]. Here, only five compartments (patella, medial tibia, medial femur, lateral tibia, and lateral femur) were evaluated because fewer findings were expected in an asymptomatic population [20]. A board certified radiologist with 13 years of experience graded cartilage lesions with scores between 1 and 6 where scores of 1 represented increased T2 signal and a sum of 6 represented lesions >75 % of thickness. Bone marrow signal changes were graded between 1 and 3 where scores of 1 represented <25 % increased T2 signal and a sum of 3 represented >50 % increase in T2 signal within the five compartments [28]. Meniscal pathology was analysed in three compartments: anterior/posterior horn and the body of each meniscus. The meniscal signal was graded between 1 and 4 where scores of 1 represented intermeniscal degeneration and a sum of 4 represented an absence of meniscal tissue [20]. Subjects with a score of two or greater in any category were excluded from analysis to reduce the potential of including subjects with early asymptomatic cartilage degeneration.

#### Segmentation and subregion division

Manual segmentations were performed to create segmentation masks by tracing the contours of the patellar, femoral, and tibial cartilage (Fig. 1) with a stylus and touchscreen monitor using Mimics software (Materialise, Plymouth, MI, USA) by three raters: a musculoskeletal radiologist with 13 years of experience [Rater 1], a biomedical engineer with 5 years of medical image analysis experience [Rater 2], and an orthopaedic surgeon with 6 years of experience [Rater 3]. Segmentations were



**Fig. 1** Example of a sagittal multi-echo spin-echo T2 acquisition with colour map overlay of the femoral, tibial, and patellar cartilage segmentation (lateral compartment, left knee)

performed on the second echo of the sagittal T2 mapping sequence on a slice-by-slice basis spanning all slices within the knee joint. To exclude synovial fluid and chemical shift artefact from the segmentations, the raters simultaneously examined the corresponding sagittal fat-suppressed SPACE sequence on a neighbouring monitor. To assess the intra-rater and inter-rater reproducibility, all raters performed manual segmentations twice for all subjects, with a delay of 1 month between segmentations.

For the selection of bone landmarks, bone contours from the T2 mapping sequence were manually segmented based on the subchondral/cortical bone dark signal, and using the segmentations, the 3D bone geometries of the femur, tibia, and patella were reconstructed in Mimics. Using a split screen view, the 3D bone reconstructions which triangulated to the second echo of the T2 image were used to choose 22 anatomical bone landmarks (Table 2), identifiable both during arthroscopy and in MRI sequences. For the eight landmarks used to describe the femur, two were placed at the most inferior and superior portion of the deepest part of the femoral trochlear groove. Two landmarks were chosen at the deepest point in the trochlea relative to the mid-plane between the condyles slightly lateral and the sulcus terminalis, at the most medial and lateral aspects. Two landmarks were chosen at the most medial and lateral aspect of the widest and most anterior portion of the intercondylar notch apex. From the posterior aspect of the femur, landmarks were placed on the medial and lateral condyle at the most posterior aspect of the cartilage margin. Eight landmarks were used to describe the tibia. A landmark was placed at the apex of both the medial and lateral tibial eminences. A landmark was placed at the most medial and lateral aspect of the tibia at the end of the cartilage margin. The remaining tibial landmarks were placed on the most posterior and anterior portion of the cartilage margin on both the medial and lateral tibial plateau. For example, on the lateral side, this point was roughly half the distance between the lateral tibial

eminence landmark and the lateral tibial landmark. Patellar landmarks included a landmark at the most inferior, superior, medial, and lateral bony portion at the cartilage margin of the bone. Two additional landmarks were placed within the line of the median patellar ridge: an inferior landmark and a superior landmark. The coordinates (x, y, z) of these landmarks were used in the custom MATLAB program (Mathworks, Natick, MA) to divide the cartilage (in detail below) into 21 clinically relevant subregions (six patellar, nine femoral, and six patellar) adapted from the ICRS Articular Cartilage Mapping System (Fig. 2) [4].

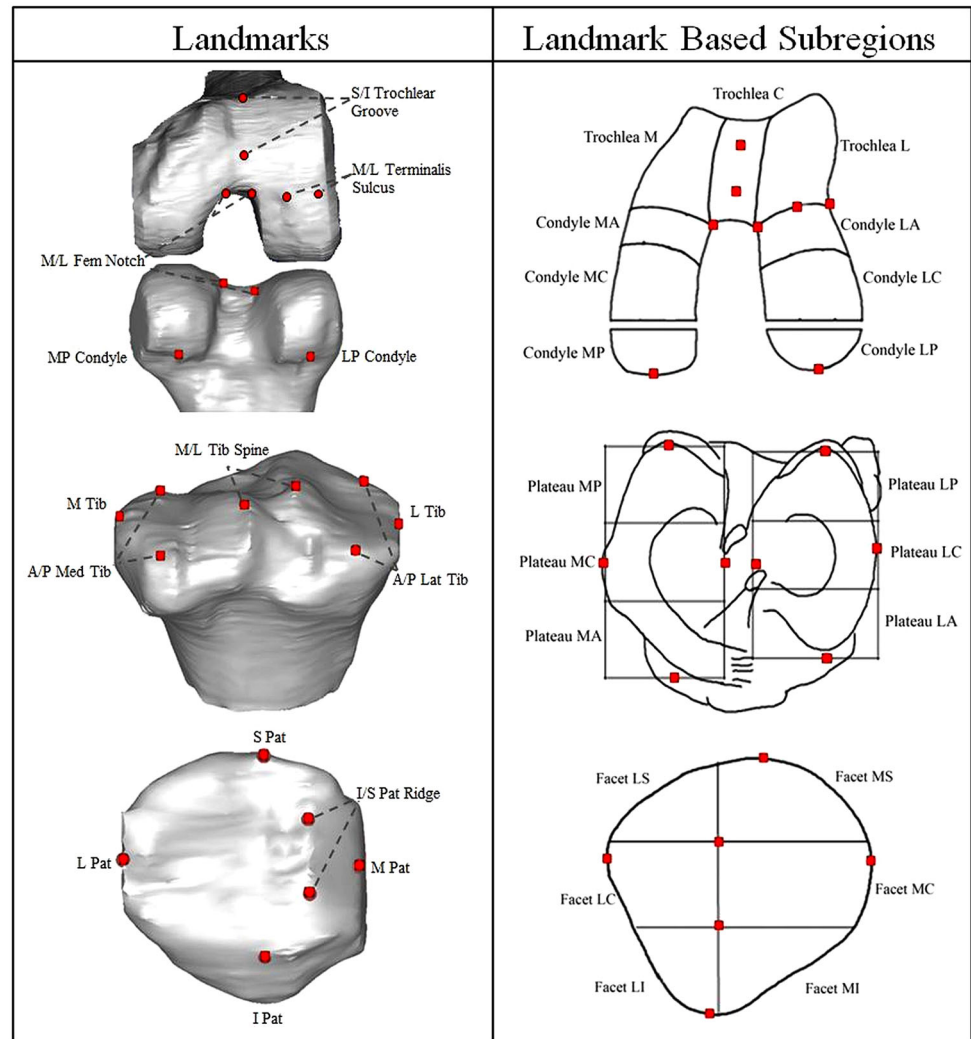
The custom MATLAB program utilized the bone landmark coordinates to divide the cartilage segmentations as follows. The femoral trochlea was separated from the lateral condyle by a line passing through two landmarks placed within the terminalis sulcus. The medial condyle was separated from the trochlea at the superior point of the intercondylar notch. The borders of the central trochlea started at the most medial and lateral points of the intercondylar notch and were parallel with the line determined by two landmarks designating the deepest part of the trochlear groove. The condyles were divided into thirds (anterior, central, and posterior). For division of the tibia, the medial and lateral tibial plateaus were divided into thirds in the anterior–posterior direction using the eminence, anterior, posterior, medial, and lateral landmarks. For the patella, the ridge landmarks were used to separate the medial and lateral facets. The facets were divided into thirds in the superior–inferior direction using the superior border and

**Table 2** Description of anatomical location of the landmarks of the femur, tibia, and patella used for subregion

Landmark	Description of anatomical location
<i>Femur</i>	
Femoral notch (med/lat)	The most superior area of the femoral notch, on the medial and lateral side
Terminalis sulcus (med/lat)	The deepest part on the medial and lateral side of the terminalis sulcus in line with the femoral notch
Trochlear groove (inf/sup)	The most inferior and superior aspect of the deepest part of the trochlear groove
Posterior condyle (med/lat)	Placed at the point where the cartilage ends on the most posterior aspect of the condyles
<i>Tibia</i>	
Tibial spine (med/lat)	The most superior portion of the medial and lateral tibial spine
Tibia (med/lat)	The most medial and lateral aspect of the tibial plateau
Medial tibia (post/ant)	The most posterior and anterior aspect of the cartilage on the medial side. Placed halfway between the medial spine and the medial tibial landmark
Lateral tibia (post/ant)	The most posterior and anterior aspect of the cartilage on the lateral side. Placed halfway between the lateral spine and the lateral tibial landmark
<i>Patella</i>	
Patella (inf/sup)	The most superior and inferior location of cartilage
Patellar ridge (inf/sup)	The most superior and inferior aspect of the patellar ridge
Patella (med/lat)	The most medial and lateral aspect of the patella

*Med* medial, *lat* lateral, *inf* inferior, *sup* superior, *post* posterior, *ant* anterior

**Fig. 2** Modified ICRS Articular Cartilage Mapping System based on landmarks and bone landmarks. Landmarks are depicted on one subject's bone model. Subregions within the femoral, tibial, and patellar cartilage were divided based on the bone landmarks (red circles; also Table 2) identified by the raters. The landmarks can be seen arthroscopically as well as within MR images (left knee). *S* superior, *I* inferior, *A* anterior, *P* posterior, *M* medial, *L* lateral, *C* central, *Fem* femoral, *Tib* tibia, *Pat* patella



the most inferior landmark of the patella located at the change in the slope of the patella.

Although the methodology was presented using a T2 mapping sequence acquired at 3.0 T MRI, the techniques described can be extrapolate to other quantitative techniques and acquisition vendors and magnet strengths.

#### *T2 map quantification*

T2 values were calculated using a Siemens WIP (work in progress) algorithm, modified from the Siemens MapIt software algorithm (Siemens Medical Solutions, Erlangen Germany). The cartilage masks were exported as binary images and imported into a custom MATLAB program with the coordinates of the landmarks and the T2 maps. The software divided the segmentation masks with the T2 overlay into the proposed 21 subregions using the 3D coordinates of the landmarks, and T2 parameters were calculated and exported to an Excel document. Only T2 values between 1.0 and 250.0 ms were included in the

analysis to exclude outliers such as synovial fluid (T2 values >250.0 ms) and T2 values rejected due to poor fit (T2 values of 0 ms).

Further subanalysis included textural analysis of the T2 values was performed using MATLAB by calculating the grey level co-occurrence matrices for each of the subregions [16]. Texture parameters of entropy, variance, contrast, and homogeneity were calculated at orientations of 0°, 45°, 90°, and 180°, with an offset of one pixel [17, 32]. The texture values at each orientation were then averaged together for each texture parameter [20].

Institutional review board (IRB) approval was obtained from the Vail Valley Medical Center (IRB# 2011-03) prior to conducting this study. All subjects provided informed consent.

#### Statistical analysis

Statistical analyses were performed using SPSS, version 20 (IBM Corporation, Armonk, NY, USA). Median T2 values

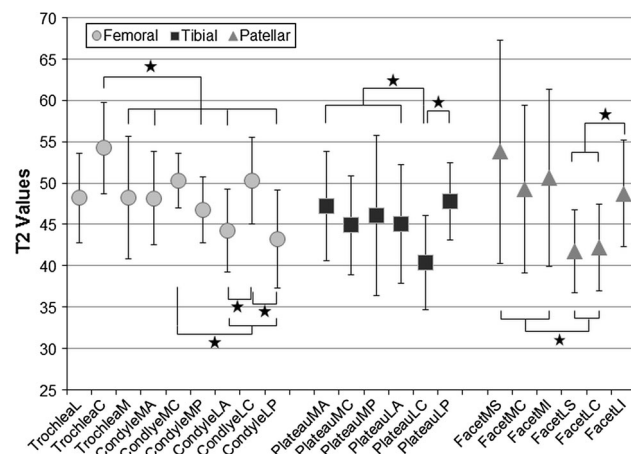
for each patient and in each subregion were compiled and used for further analysis. A repeated measures ANOVA was used to compare means (of median T2 values) between subregions separately. Bonferroni corrections were applied to post hoc comparisons between subregions. The mean texture parameters of entropy, variance, contrast, and homogeneity were compared between subregions. To assess the repeatability of the segmentations in a manner that could be generalized to a single future rater from the population of qualified raters, a two-way random effects model calculated the single measures intra-class correlation coefficient (ICC) for each subregion’s median T2 value. The ICC values were graded using the scoring method described by Fleiss et al.: 0.75–1.00 = excellent reliability, 0.40–0.75 = fair to good reliability, 0–0.40 = poor reliability [10]. The root mean square coefficient of variation (RMSCV) was also calculated to assess rater reliability [14].

**Results**

Seven subjects had a WORMS score of two or greater in at least one region and thus were not considered entirely healthy and were excluded from analysis.

**T2 values**

The averages ( $\pm$ STD) of the median T2 values for each subregion are demonstrated in each subregion (Fig. 3). Within each subregion, the median T2 value was chosen to summarize the T2 measurements. Subsequent comparison



**Fig. 3** Averages of median T2 values ( $\pm$ STD) in subregions within the femoral, tibial, and patellar cartilage in asymptomatic volunteers. *S* superior, *I* inferior, *A* anterior, *P* posterior, *M* medial, *L* lateral, *C* central. Stars indicate significance ( $P \leq 0.05$ ) between subregions. Significant differences between femoral, tibial, and patellar subregions were not analysed

testing between subregions utilized these median values as data (“Appendix”). The median T2 values, averaged across subjects, ranged from 43.2 to 54.2 ms in the femur, 40.3 to 48.0 ms in the tibia, and 40.3 to 47.2 ms in the subregions of the patella.

**Texture analysis: subanalysis of T2 values**

Mean contrast, entropy, homogeneity, and variance for the T2 measurements in each subregion are presented (Fig. 4a–d). Further subregion analysis is described in detail below (“Appendix”).

Within the femoral cartilage, the central trochlea had higher variance ( $P < 0.05$ ) and entropy ( $P < 0.001$ ) than the medial trochlea. Both the central and lateral trochlea had higher entropy than all other regions ( $P < 0.05$ ) except the central lateral condyle. The central medial subregion of the femoral condyles had significantly higher variance than both the medial ( $P < 0.001$ ) and lateral ( $P < 0.05$ ) posterior regions of the condyles.

Within the tibial plateaus, the central regions had significantly higher entropy than the anterior and posterior regions ( $P < 0.001$ ), except for the lateral posterior region which was not significantly different. The central lateral region also had lower variance ( $P < 0.05$ ), higher homogeneity ( $P < 0.05$ ), and lower contrast ( $P < 0.05$ ) than each of the other tibial subregions.

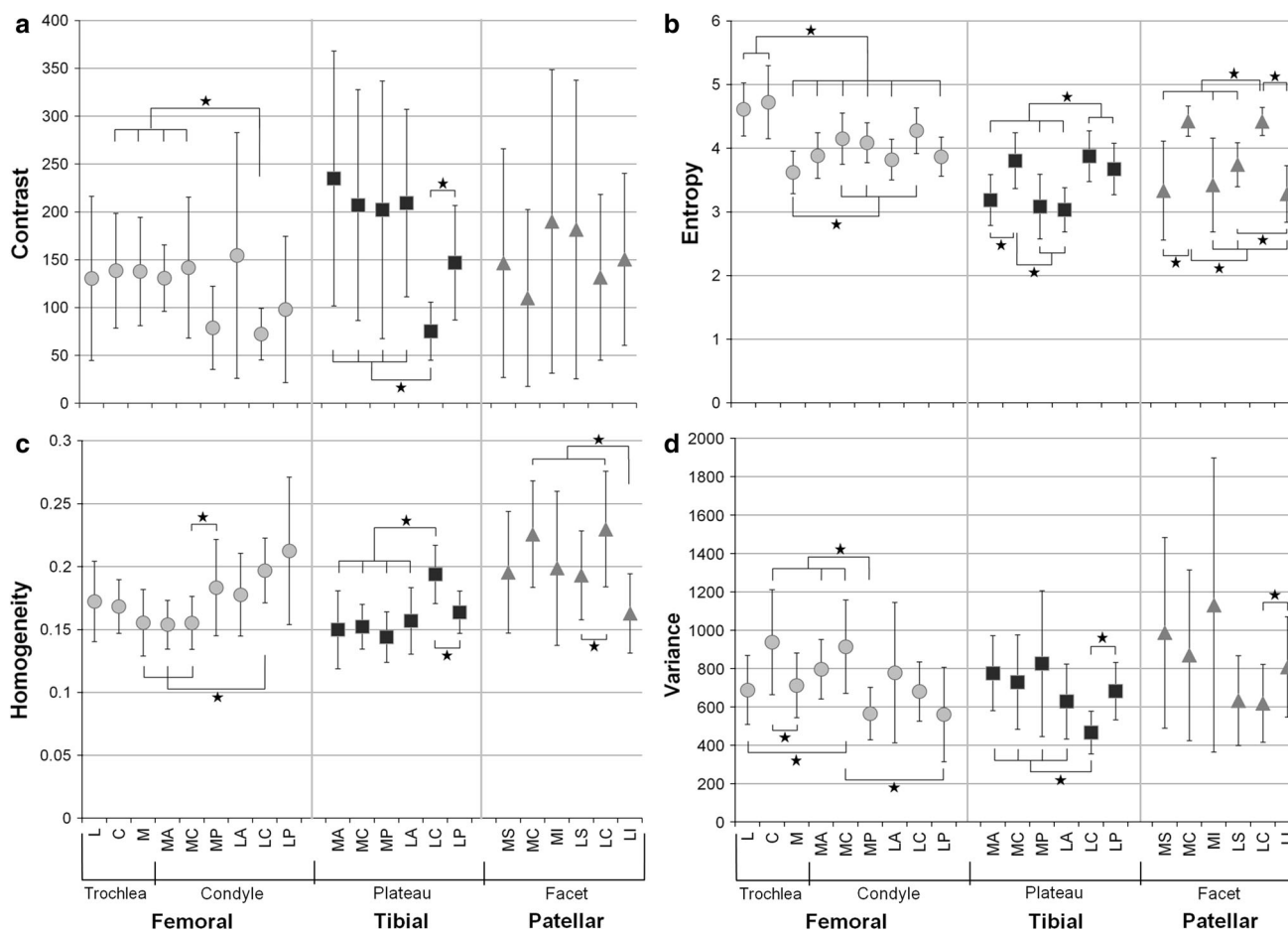
For the patellar subregions, both the medial and lateral central regions had higher entropy ( $P < 0.001$ ) than the superior and inferior regions. Homogeneity was significantly higher in the central lateral facet when compared to the superior lateral facet ( $P < 0.05$ ) and the inferior lateral facet ( $P < 0.001$ ).

**Intra-class correlation coefficients (ICC)**

The inter-rater and intra-rater ICC values are reported in Table 3. Inter-rater and intra-rater ICC values showed either “excellent” or “fair to good” agreement (13 subregions with excellent agreement and eight subregions with fair to good agreement) between and within the three raters.

**Discussion**

The most important finding of the present study was that significant differences in median T2 values and texture parameters were observed within clinically relevant subregions of the femoral, tibial, and patellar cartilage, confirming our hypothesis by demonstrating that there are normal variations of T2 values within the screened asymptomatic knee joint. This implies that there is not just



**Fig. 4** Mean contrast of cartilage T2 ( $\pm$ STD) (a), mean entropy of cartilage T2 ( $\pm$ STD) (b), mean homogeneity of cartilage T2 ( $\pm$ STD) (c), and mean variance of cartilage T2 ( $\pm$ STD) (d) in subregions within the femur, tibia, and patella in asymptomatic volunteers.

S superior, I inferior, A anterior, P posterior, M medial, L lateral, C central. Star indicates significance ( $P \leq 0.05$ ) between subregions. Significant differences between femoral, tibial, and patellar subregions were not analysed

one single T2 value for asymptomatic cartilage within the knee, confirming our hypothesis that subregions are an important consideration for analysis to locate natural variations of T2 values within a joint. The overall high inter-rater and intra-rater repeatability supports the robustness of the manual segmentation, selection of bone landmarks, and the resulting division based on our proposed clinically relevant ICRS-based subregions. Defining subregions based on an accepted method, such as the ICRS articular cartilage mapping system, may make the data more universally applicable to better integrate quantitative mapping from theory to practise in the clinical workflow.

Rather than evaluating the mean of the T2 values for the entire knee, this study summarized the central tendency of the values within each individual subregion by evaluating the median T2 values and averaging the medians within each subregion across subjects. While previous studies have calculated the mean within subregions, we advocate

using the statistical median because it is more robust against outliers, such as areas of image misregistration between fat and water on MRI (i.e. chemical shift artefact) and synovial fluid that may have been manually segmented into the subregions. Additionally, for analysis, a T2 value cutoff of 1.0–250.0 ms was chosen to further exclude synovial fluid and chemical shift artefact which have high T2 values, and T2 values rejected due to poor fit (0 ms). This range may be appropriate for future studies, including patients with chondral damage who may as a result of pathology have increased fluid and inherently higher T2 values [15].

It is theorized that some of the observed differences in T2 values between subregions had clinical relevance because of the high T2 values observed in areas of joint loading and regions which commonly develop OA. Elevated T2 values in the central femoral condyles were consistent with what has been described in the literature

**Table 3** Intra-rater and inter-rater intra-class correlation coefficients (ICC) for each subregion

Subregion name	Inter-rater Reliability (ICC*)	Intra-rater 1	Intra-rater 2	Intra-rater 3
<i>Femur</i>				
TrochleaL	0.45 [0.21, 0.68]	0.93	0.68	0.71
TrochleaM	0.39 [0.14, 0.63]	0.89	0.44	0.65
TrochleaC	0.41 [0.17, 0.65]	0.68	0.3	0.67
CondyleMA	0.55 [0.31, 0.75]	0.86	0.53	0.76
CondyleMC	0.82 [0.68, 0.91]	0.93	0.72	0.92
CondyleMP	0.89 [0.79, 0.94]	0.79	0.9	0.94
CondyleLA	0.45 [0.21, 0.68]	0.79	0.74	0.64
CondyleLC	0.85 [0.74, 0.93]	0.94	0.76	0.95
CondyleLP	0.79 [0.65, 0.90]	0.93	0.79	0.87
<i>Tibia</i>				
PlateauMA	0.70 [0.51, 0.84]	0.88	0.77	0.85
PlateauMP	0.78 [0.62, 0.89]	0.92	0.76	0.72
PlateauMC	0.87 [0.77, 0.94]	0.88	0.89	0.82
PlateauLA	0.17 [−0.06, 0.44]	0.76	0.56	0.65
PlateauLP	0.69 [0.50, 0.84]	0.76	0.66	0.87
PlateauLC	0.67 [0.47, 0.82]	0.89	0.56	0.76
<i>Patella</i>				
FacetMS	0.58 [0.35, 0.76]	0.71	0.44	0.76
FacetMC	0.80 [0.65, 0.90]	0.94	0.62	0.88
FacetMI	0.69 [0.50, 0.84]	0.79	0.5	0.93
FacetLS	0.89 [0.80, 0.95]	0.95	0.87	0.92
FacetLC	0.83 [0.70, 0.92]	0.94	0.83	0.93
FacetLI	0.85 [0.73, 0.93]	0.96	0.83	0.91

\* 95 % confidence intervals for inter-rater reliability ICCs [LB, UB]

and are a reported common area for development of OA [12, 13, 27, 33]. The central trochlea also had significantly elevated T2 values than nearly all femoral subregions and is another common reported area for OA development [30]. On the lateral plateau of the tibia, the anterior and posterior regions had significantly higher T2 values than the central lateral plateau region. The lower values in the central lateral tibial plateau were unexpected because this was a subregion we thought would have higher T2 values because this is another common area for OA development. We can hypothesize that perhaps this is the result of the different loading conditions from the contact between two convex surfaces causing a change in biochemical structure within the cartilage. Moreover, during arthroscopy, the central lateral plateau commonly appears soft to manual probing and there is commonly signal change reported in MRI images within this region [27, 36]. Using the ovine model, it has been reported that the lateral tibial plateau experienced an increase in joint contact

stress which led to cartilage fibrillation, proteoglycan loss, and collagen breakdown in the lateral subregions [24]. Likewise, Maher et al. [24] observed an increase in T2 values in these subregions which corresponded to the higher contact pressures.

In the patella, the T2 values were higher and had larger standard deviations, especially in the medial facet, perhaps due to partial volume averaging with adjacent tissue and synovial fluid. The raters reported some difficulty segmenting the bone–cartilage interface on the sagittal scan which appeared thickened. In imaging, partial volume averaging occurs when multiple tissue types are encompassed within a single voxel, such as fat and water, or can occur when the structure is oriented obliquely to the imaging plane. The patella tends to normally tilt laterally causing the medial facet to align more obliquely within the sagittal plane of the scan, probably causing this to occur [19].

Texture analysis using grey level co-occurrence matrix texture features may be more sensitive to early changes in cartilage degeneration than the absolute mean T2 value because it analyses the distribution of each value in a subregion, using the grey values that make up the image, rather than combining the values into one mean value allowing for detection of slight changes. No studies were found in the literature which compared texture analysis results within subregions in a healthy cohort. The observed differences in texture parameters were in regions that have been reported to commonly develop OA such as the central trochlea, the medial femoral condyles, and the central tibia plateaus. The central trochlea had higher variance and entropy than the medial trochlea. High entropy signifies more conformity in neighbouring pixels. Blumenkrantz et al. [3] demonstrated that the measure of entropy was significantly higher in osteoarthritic cartilage compared to age-matched controls in the knee. High variance demonstrates a high dispersion of grey level pixel values around the mean, whereas high contrast signifies that many pixels with different values are detected to be neighbouring, each of which has been shown to be elevated in osteoarthritic cartilage [5, 22]. The findings may be due to the known anisotropy of cartilage. Anisotropy, or having different values in different directions, is lessened on a biochemical level with the early damage due to OA, making the cartilage more heterogeneous and may lend an explanation to the higher entropy, variance, and contrast values [5]. Interestingly, the central lateral tibial plateau had lower variance, higher homogeneity, and lower contrast than the remaining tibial subregions which was consistent with the finding of lower median T2 values in this subregion potentially inferring



that in our healthy population, the cartilage was more heterogeneous even in this highly loaded subregion.

While several studies have reported T2 values using larger, gross subregions than presented in the present study, the different subregions make direct comparison to other findings difficult [7, 8, 31]. A standardized set of clinically relevant subregions for analysis, such as our proposed subregions, is necessary for comparison between research centres and implementation of T2 mapping into standard clinical practice. The subregions proposed in this study were modified from the ICRS articular cartilage mapping system, which is used for documenting arthroscopic findings. The main modification to this system was that the patella was separated into medial and lateral along the patellar ridge, rather than dividing it into medial, central, and lateral subregions. We theorized that this would increase reproducibility due to the ease of detecting the patellar ridge, whereas the central region is difficult to assign because of significant known anatomical variation of the patella between subjects.

While T2 mapping was used, it is possible that other quantitative cartilage mapping techniques may be more sensitive to early cartilage degeneration. In particular, T2 mapping is not sensitive to proteoglycan (PG) concentration, which is one of the earliest biochemical changes that occur with cartilage degeneration [29]. T1-weighted mapping sequences have been reported to be sensitive to changes in PG concentration thus may be more sensitive to early cartilage degeneration [21]. However, T2 mapping is currently the most widely available noninvasive mapping technique as most MRI manufacturers offer the sequence, and the image is acquired without the use of contrast agents. Moreover, the methodology presented in this study with the subregion definition based on bone landmarks reproducibly identifiable by arthroscopy, and imaging can be applied to any quantitative mapping parameter that should prove ultimately to be optimal.

The clinical relevance of this work is that it defines that there are differences in subregions of articular cartilage in biochemical composition, structure, and content of the knee joint. This indicates that all subregions of the knee are unique in their make-up and that further study is warranted as to the implications on both MRI evaluation and possibly resurfacing procedures. Limitations of this study include difficulty in assuring that asymptomatic volunteers have no early cartilage degeneration. Arthroscopy remains the gold standard in cartilage evaluation but is not reasonable to use in this population. Conventional methods for detecting cartilage

damage are not sensitive enough for detecting early OA, which makes determining specific T2 values for healthy cartilage complicated. For the present study, inclusion/exclusion criteria were very rigorous and WORMS assessment was used to further exclude volunteers with bone oedema and degeneration in the cartilage and intra-substance meniscal degeneration and tears of the menisci.

The study was limited by the manual nature of the methodology. Manual segmentation and manual landmark selection were used which is too time intensive for inclusion clinically. However, automated cartilage segmentation and registration onto T2 maps may be available in the near future, and reproducible T2 mapping can be implemented into standard clinical care workflow [34].

## Conclusion

This study demonstrated characteristic patterns of cartilage T2 mapping in clinically relevant articular cartilage subregions of the femur, tibia, and patella. While T2 mapping was used in the present study, the methodology proposed can be easily implemented in any other imaging biomarker of interest. The proposed subregions based on the ICRS articular cartilage mapping system may increase the efficacy and reproducibility of quantitative mapping and may make the data transferrable across centres and among orthopaedists and radiologists to better integrate quantitative mapping from theory to practise in the clinical routine.

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## Appendix

See Table 4.

**Table 4** Mean  $\pm$  standard deviation (SD) within each subregion for all T2 measurements

Subregion name	T2 values		Contrast		Entropy		Homogeneity		Variance	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<i>Femur</i>										
TrochleaL	48.2	5.4	130.5	85.8	4.61	0.42	0.17	0.03	688.7	179.9
TrochleaC	54.2	5.5	138.7	60.0	4.72	0.57	0.17	0.02	938.0	273.7
TrochleaM	48.3	7.4	137.9	56.5	3.62	0.33	0.16	0.03	712.7	168.9
CondyleMA	48.2	5.7	130.9	34.6	3.89	0.36	0.15	0.02	797.0	154.8
CondyleMC	50.3	3.3	142.0	73.6	4.15	0.40	0.16	0.02	914.3	243.5
CondyleMP	46.8	4.0	78.9	43.4	4.09	0.31	0.18	0.04	565.7	136.9
CondyleLA	44.2	5.0	154.6	128.5	3.82	0.32	0.18	0.03	779.3	365.8
CondyleLC	50.3	5.2	72.4	27.0	4.28	0.36	0.20	0.03	680.6	154.0
CondyleLP	43.2	5.9	98.2	76.5	3.87	0.31	0.21	0.06	561.0	246.3
<i>Tibia</i>										
PlateauMA	47.2	6.6	235.1	133.1	3.19	0.40	0.15	0.03	776.3	195.3
PlateauMC	44.9	6.0	207.2	120.6	3.81	0.44	0.15	0.02	729.7	246.4
PlateauMP	46.1	9.7	202.2	134.6	3.09	0.51	0.14	0.02	826.4	380.1
PlateauLA	45.0	7.2	209.4	97.9	3.03	0.35	0.16	0.03	628.4	195.0
PlateauLC	40.3	5.7	75.4	30.3	3.88	0.40	0.19	0.02	466.3	111.5
PlateauLP	47.8	4.7	147.0	59.7	3.68	0.40	0.16	0.02	682.6	149.1
<i>Patella</i>										
FacetMS	53.8	13.5	146.6	119.5	3.34	0.77	0.20	0.05	986.8	497.7
FacetMC	49.3	10.1	110.1	92.4	4.43	0.24	0.23	0.04	870.2	445.1
FacetMI	50.6	10.7	190.1	158.7	3.42	0.74	0.20	0.06	1,131.3	765.7
FacetLS	41.7	5.0	181.8	156.1	3.74	0.34	0.19	0.04	633.1	234.6
FacetLC	42.2	5.2	131.7	86.6	4.42	0.22	0.23	0.05	619.3	202.9
FacetLI	48.7	6.5	150.6	89.8	3.28	0.44	0.16	0.03	808.9	261.8

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