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The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee

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Summary

Objectives—To report on the process and criteria for selecting acquisition protocols to include in the osteoarthritis initiative (OAI) magnetic resonance imaging (MRI) study protocol for the knee.

Methods—Candidate knee MR acquisition protocols identified from the literature were first optimized at 3 Tesla (T). Twelve knees from 10 subjects were scanned one time with each of 16 acquisitions considered most likely to achieve the study goals and having the best optimization results. The resultant images and multi-planar reformats were evaluated for artifacts and structural discrimination of articular cartilage at the cartilage–fluid, cartilage–fat, cartilage–capsule, cartilage–meniscus and cartilage–cartilage interfaces.

Results—The five acquisitions comprising the final OAI MRI protocol were assembled based on the study goals for the imaging protocol, the image evaluation results and the need to image both knees within a 75 min time slot, including positioning. For quantitative cartilage morphometry, fat-suppressed, 3D dual-echo in steady state (DESS) acquisitions appear to provide the best universal cartilage discrimination.

Conclusions—The OAI knee MRI protocol provides imaging data on multiple articular structures and features relevant to knee OA that will support a broad range of existing and anticipated measurement methods while balancing requirements for high image quality and consistency against the practical considerations of a large multi-center cohort study. Strengths of the final knee MRI protocol include cartilage quantification capabilities in three planes due to multi-planar reconstruction of a thin slice, high spatial resolution 3D DESS acquisition and the multiple, non-fat-suppressed image contrasts measured during the T2 relaxation time mapping acquisition.

Keywords

Osteoarthritis; Knee; MRI; Protocol

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Background

Osteoarthritis (OA) of the knee is a significant contributor to disability and loss of independence among middle age and elderly persons and presents a clear and growing public health need (<http://www.cdc.gov/nchs/fastats/arthritis.htm>). Because of the chronic nature of OA and its variable clinical outcomes, the use of clinical endpoints in studies of risk and prognostic factors and in clinical trials that test interventions to prevent or slow the progression of this disease requires studying large numbers of patients for long periods of time, often at great expense. Developing effective medical treatments to prevent or to reduce progression of OA is hampered by the lack of robust biomarkers of disease onset and progression.

The osteoarthritis initiative (OAI) is a public–private partnership jointly sponsored by the National Institutes of Health (NIH), including the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute on Aging (NIA), National Institute of Dental and Craniofacial Research (NIDCR), National Center for Complementary and Alternative Medicine (NCCAM), Office of Research on Women’s Health (ORWH), National Institute of Biomedical Imaging and Bioengineering (NIBIB), and National Center on Minority Health and Health Disparities (NCMHD), and the pharmaceutical industry. The OAI is focused on identifying the most promising biomarkers of development and progression of symptomatic knee OA. A total of 4796 men and women, aged 45–79 years, who either have or are at increased risk of developing knee OA have been enrolled in the study. Annual radiography and magnetic resonance imaging (MRI) of the knee and clinical assessments of disease activity are being performed in all participants over a period of 4 years. Genetic and biochemical specimens are also being collected annually from all participants.

A primary objective of the OAI is to create a public resource for identifying, characterizing and validating a broad range of imaging biomarkers for OA of the knee that could be used to investigate basic research hypotheses as well as to serve as outcomes in clinical trials of new therapies. Accordingly, the goals for the OAI MRI study protocol are to (1) provide imaging data on as many articular structures and features believed to be relevant to knee OA as possible; (2) provide images that are able to support as broad a range of existing and anticipated measurement methods for each of these structures and features as possible; and (3) balance scientific requirements for image quality and consistency against the need to maintain high throughput of the participants and the ability of the participants to tolerate the annual MRI examinations.

The report outlines the rationale used by the OAI Imaging Working Group, which included scientists and clinicians from academia and industry with expertise in MRI of OA and cartilage (see *Acknowledgements*), to address these design considerations and ultimately to arrive at the knee MRI protocol used in the OAI. This report is not intended to serve as a review of the literature on existing or emerging imaging biomarkers of knee OA using MRI technology. Several excellent reviews have recently been published, and readers are referred to these for broad overviews of the field¹⁻⁵.

A key consideration in protocol development for the OAI was to identify which knee OA features to target. Since OA affects several articular structures, and is believed to progress through multiple pathogenic pathways, the imaging protocol had to support multi-feature, structural assessment of the knee. The OAI Imaging Working Group prioritized the following knee structures: articular cartilage, osteophytes, bone marrow abnormality (BMA), bone attrition and cysts, the osteochondral junction (bone surface area), meniscal integrity, synovial tissue, joint effusion, anterior cruciate ligament (ACL) and posterior

cruciate ligament (PCL), medial collateral ligament (MCL) and lateral collateral ligament (LCL). Quantitative assessment of articular cartilage morphology (e.g., volume, thickness, cartilaginous/denuded surface area, *etc.*) was considered to be particularly important. Many assessments of the selected knee structures have been previously validated using MRI at 1.5 T, and are used widely clinically and in research⁶⁻¹⁴.

The above priorities determined that anatomical coverage had to include at least the entire patellar, femoral and tibial cartilages but ideally the entire synovial cavity. Other decisions with respect to acquisition planes, spatial resolution, image contrast, and acquisition time are discussed below, but the general principles underlying the tradeoffs are outlined in a report from the Workshop on Imaging Osteoarthritis of the Knee¹⁵, held on December 5–6, 2002 in Bethesda, MD by Outcome Measures in Rheumatology Clinical Trials (OMERACT) and Osteoarthritis Research Society International (OARSI).

Early in the planning stages of the OAI, the decision was made to purchase dedicated, state-of-the-art MRI systems for each of the four study sites (The Ohio State University, Columbus, OH; University of Maryland, School of Medicine, Baltimore, MD; University of Pittsburgh, Pittsburgh, PA; and Memorial Hospital of Rhode Island, Pawtucket, RI) to minimize acquisition variability and accommodate the large number of subjects to be examined over the course of the study. In 2003, when the OAI study was being designed and implemented, 3 Tesla (T) MRI systems had recently been introduced to the commercial market but were not yet routinely available in clinical settings. MRI at 3 T offered potential advantages over 1.5 T in terms of signal level that could be traded for increased signal-to-noise (SNR), spatial resolution or imaging speed. This advantage was felt to be particularly useful for T2 relaxation time measurement of cartilage^{2,10,16,17} and was believed to outweigh potential disadvantages of high field strength, such as increased susceptibility to metallic artifacts, increased fat-water chemical shift, and different tissue relaxation times than those observed at 1.5 T^{18,19}. In spite of the relative lack of clinical and research experience at 3 T, it was understood that 1.5 T knee MRI protocols would not translate directly to 3 T without adjusting for the differences detailed above. Other important considerations for the OAI included: use of commercially available, food and drug administration (FDA)-approved, pulse sequences and radiofrequency (RF) coils; minimizing redundancy among acquisitions in the measurements that could be derived from them; the need to position and image both knees within 75 min to prevent subject discomfort and minimize the risk of dropout; and minimizing individual sequence acquisition times to reduce the possibility of motion artifacts and associated image degradation, especially for 3D acquisitions and 2D multi-echo spin-echo (MESE) acquisitions.

The process of meeting these diverse goals with a single, uniform protocol entailed selecting the image contrasts most likely to satisfy the anticipated needs and making careful tradeoffs in image spatial resolution and tissue contrasts. To facilitate this process, a pilot study was undertaken in which selected candidate acquisition sequences, based on contrast parameters at 1.5 T, were optimized for use at 3 T. A small sample of knees was then scanned with the most promising acquisitions and the resulting images visually evaluated by musculoskeletal imaging experts affiliated with the OAI (see *Acknowledgements*) for suitability in cartilage segmentation and semi-quantitative assessments of relevant tissues. Details of this pilot study and its results can be found on the OAI website (<http://www.oai.ucsf.edu>).

The OAI MRI protocol

The final OAI knee MRI protocol is shown in Tables I and II. Subject positioning and scan set up can be found in detail in the OAI MRI Operator's Manual available on the website (<http://www.oai.ucsf.edu>). The knee MRI acquisition begins with a three-plane localizer,

followed by a coronal intermediate-weighted (IW) 2D turbo spin-echo (TSE) (COR IW 2D TSE)⁷ for evaluating the MCL and LCL, marginal femoral and tibial osteophytes, the medial and lateral meniscal body segments, and the presence/extent of subchondral bone cysts and bone attrition. All 2D and 3D coronal acquisitions are oriented coronal to the joint based on anatomic landmarks using a double oblique prescription (Figs. 1 and 2)⁹ in order to improve the reproducibility of cross-sectional anatomy depicted on serially acquired MRI exams.

The coronal plane^{1,9,15} is excellent for evaluating articular cartilage along the central weight-bearing surfaces of the femur and tibia, where the cartilage curves up the tibial spines and the corresponding curves of the adjacent femoral condyles near the notch. This plane is also excellent for delineating the osteochondral junctions at the medial and lateral margins of the femur and tibia. Intermediate weighting⁷ is used in COR IW 2D TSE to balance the need for an echo time (TE) short enough to detect non-displaced meniscal tears but still long enough to discriminate articular cartilage. Because of the high density and linear orientation of collagen fibers in the MCL and LCL, these structures show very rapid T2 relaxation and therefore good delineation with intermediate-TE sequences.

Although the 3D dual-echo in steady state (DESS) image contrast²¹ has not been as extensively evaluated for quantitative cartilage measurements as have fat-suppressed 3D fast low-angle shot (FLASH) or 3D spoiled gradient-recalled echo (SPGR) image contrast, 3D DESS with selective water excitation (WE) appeared to show better cartilage discrimination in pilot scans using volunteer subjects, and therefore was included in the OAI MRI protocol. Sagittal (SAG) 3D DESS WE was found not only to provide excellent cartilage delineation for morphological measurements, such as total joint cartilage thickness and volume, it also delineates osteophytes along the anterior and posterior margins of the femur and tibia and the superior and inferior margins of the patella with high resolution, shows tears of the anterior and posterior horns of the menisci, depicts subarticular bone cysts and bone attrition, and assesses integrity of the ACL and PCL and the patellar and quadriceps tendons^{1,15}. In addition, the SAG 3D DESS acquisition is faster than an equivalent 3D FLASH (or SPGR) acquisition; the resultant time savings can be potentially traded for increased SNR or spatial resolution. All 2D and 3D sagittal acquisitions are oriented sagittal to the joint based on anatomic landmarks and are orthogonal to the coronal acquisitions (Figs. 3 and 4).

The 3D DESS WE acquisition selected uses 0.7 mm thick slices. Thinner slices could have been obtained, however, the cost in increased scan time and subsequent loss of SNR was considered to be excessive. The 3D FLASH WE acquisition, in contrast, uses 1.5 mm slices, as was the coronal slice thickness that was previously validated at 1.5 T^{3,11,12,22,23}. Because the SAG 3D DESS WE acquisition has thin slices, the resultant images can also be reformatted (MPR) into the coronal and axial planes (Figs. 5 and 6) to display optimally the tibial and central weight-bearing surface of the femoral cartilage, as well as the trochlear and patellar cartilage, respectively^{1,3,6,11,13}. The multiplanar reformation (MPR) images can be of variable slice thickness; 1.5 mm was chosen for the OAI to enable comparison with the previously validated coronal 3D FLASH images. Other MPR orientations and slice thicknesses can be retrospectively calculated from the sagittal images. However, the in-plane spatial resolution of the MPR images is governed by the size and orientation of the voxels in the original acquisition. The SAG 3D DESS WE series utilizes near anisotropic voxels (0.7 mm slice thickness × 0.37 mm × 0.46 mm) to maximize in-plane sagittal spatial resolution in a reasonable acquisition time (10.5 min). The resultant in-plane coronal MPR spatial resolution is thus 0.7 mm × 0.37 mm.

The COR T1-weighted (T1W) 3D FLASH WE acquisition also provides high-resolution delineation of articular cartilage⁹, and as noted above has been extensively validated at 1.5 T

and shown to support accurate quantification of the volume and thickness of cartilage over the tibial plateaus and the central surface of the femur^{3,11,12}. Since the OAI MRI protocol was designed and implemented, 3D FLASH WE at 3 T has been cross-validated with 3D FLASH WE at 1.5 T for quantitative analysis of cartilage morphology^{23,24}.

The OAI protocol also includes SAG IW 2D TSE fat suppression (FS), which provides excellent assessment of the ACL and PCL, the anterior and posterior horns of the menisci, anterior and posterior osteophytes, synovial effusion and peri-articular cysts and bursae. This technique also delineates articular cartilage; although, not as well as the 3D acquisitions do. To obtain relatively high spatial resolution in a relatively short acquisition time, the field of view (FOV) was made smaller (16 cm) than desired (24 cm) for complete coverage of the synovial cavity. The unique contribution of the SAG IW 2D TSE FS acquisition to the protocol is its sensitivity to BMA and subchondral cysts^{1,25-27} (Fig. 7A). Gradient-echo (GRE) techniques, such as 3D DESS (Fig. 7B) and 3D FLASH (Fig. 7C), even with robust FS, are relatively insensitive to BMA (large arrow in Fig. 7A). They are, however, sensitive for subchondral cysts (thin arrow).

Finally, SAG 2D MESE is included in the protocol to allow quantification of cartilage T2 relaxation times as well as to provide a range of non-fat-suppressed image contrasts (proton density [PD], IW, T2-weighted [T2W]) (Fig. 8) to improve assessment of many joint components, including ligaments and tendons, and the cartilage–bone interface. T2 relaxation times are believed to relate to the integrity of cartilage matrix, particularly collagen, and therefore to be potentially useful for evaluating early degeneration^{2,10,16}.

Based on the acquisition time constraints, the OAI Imaging Working Group decided that it was not feasible to obtain all acquisitions in the final protocol on both knees. Accordingly, two acquisitions were excluded from the left knee examination (Table I) unless subjects had surgical hardware in the right knee, in which case, the two sequences would be performed on the knee without surgical hardware. Subjects with unilateral knee arthroplasty would have no MRI examinations of the operated knee.

COR T1W 3D FLASH WE was elected to be acquired on only one knee because SAG 3D DESS WE was considered to provide better contrast for delineating the interface between articular cartilage and a range of degenerated and normal tissues, as well as better contrast for evaluating menisci, ligaments and synovial effusion. In pilot scans of volunteer knees, the cartilage–capsule and cartilage–cartilage interfaces (Fig. 4) were often difficult to discriminate with 3D FLASH WE, but were well discriminated with 3D DESS WE. Both 3D FLASH WE and 3D DESS WE were felt to provide excellent delineation of osteophytes, however, the most important contribution of SAG 3D DESS WE in this protocol is high-resolution delineation of articular cartilage.

3D FLASH WE and 3D DESS WE have subsequently been cross-validated at 3 T for cartilage volume quantification²⁸⁻³⁵. The absolute value performance and test–retest precision of the direct SAG 3D DESS and the coronal MPR DESS image series were found to be comparable to that provided by coronal 3D FLASH in a cross-sectional analysis. These results, and the history of use in knee OA studies, support the decision to include COR T1W 3D FLASH WE in the OAI MRI protocol. However, insufficient acquisition time was available to perform this technique in both knees. Similarly, SAG 2D MESE was performed on only one of the two knees to meet imaging time constraints. Finally, the Imaging Working Group felt that axial MPR of the high-resolution SAG 3D DESS WE would provide sufficient visualization of the patellofemoral joint in a plane orthogonal to the cartilage plate, and therefore excluded direct axial imaging of either knee.

Total imaging time for the final OAI knee MRI protocol is 58 min (Table I), leaving 17 min for subject positioning, coil placement and for scan prescription to stay within the total examination time limit of 75 min for both knees.

Conclusion

In summary, the OAI MRI protocol offers a balance between the scientific and practical considerations in assessing the key articular structures and features believed to be involved in the development and progression of OA in the knee. While implementation of such a long and rigorous MRI protocol may not be feasible in the clinic or in all clinical trials, it is hoped that OAI will help guide the development of more streamlined protocols applicable for use at either 3 T or 1.5 T.

Several limitations of the protocol development process should be noted. We were limited to the acquisition and analysis methods which had been validated as of 2003. Although other MRI biomarkers that relate to cartilage matrix damage^{2,5,20,36,37} and subchondral trabecular architecture and bone volume¹⁴ have been described, the current OAI MRI protocol does not have sufficient imaging time to support those measurements and still satisfies its primary scientific objectives. Given time constraints for planning and startup of the OAI, the knee MRI protocol was finalized and implemented without formally assessing the performance characteristics of any biomarker measurements, such as cartilage volume, semi-quantitative assessments of articular lesions, *etc.* Since the OAI protocol was implemented, several studies of quantitative cartilage morphology using images acquired with the OAI protocol and addressing measurement precision, 3D FLASH vs 3D DESS comparisons and sensitivity to change have been published^{28-35,38,39}. These performance parameters will continue to be important topics for investigation.

No external validation (compared to cadaver or arthroscopy) of cartilage measurements or assessments has been done using the OAI MRI protocol or any other acquisition protocol at 3 T. Key parameters (e.g., spatial resolution) of the 3D FLASH acquisitions included in the OAI protocol were identical to those previously validated at 1.5 T for quantitative cartilage measurements compared to cadaver knees¹². Moreover, 3D FLASH acquisitions acquired with the same resolution at 1.5 T and 3 T gave identical precision for quantitative cartilage measurements²³. We have no reason to believe that external validation results would differ between 3 T and 1.5 T acquisitions, but studies are needed to confirm this.

The OAI clinical data set as well as the radiographic and MRI images are available through the study's public website (www.oai.ucsf.edu). It is hoped that the OAI MRI images will support not only the majority of analysis methods and imaging biomarker measurements that are currently available but many of those yet to be developed. We urge users of the OAI public data to employ a systematic framework, such as the OMERACT filter⁴⁰, to the development and validation of imaging biomarkers of OA. The availability of these images to the general community of investigators should serve to accelerate research in OA and thus our understanding of this enigmatic disease and how to combat it.

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Abbreviations

COR	coronal
CNR	contrast-to-noise ratio
DESS	dual-echo steady state
ETL	echo-train length
FDA	food and drug administration
FLASH	fast low-angle shot
FOV	field of view
FS	fat suppression
GRE	gradient-echo
IW	intermediate-weighted
MEMS	multi-echo, multi-slice
NEX	number of excitations
MPR	multiplanar reformation
PD	proton density
SAG	sagittal
SE	spin-echo
SNR	signal-to-noise ratio
SPGR	spoiled gradient-recalled echo
T1W	T1-weighted

T2W	T2-weighted
TE	echo time
TR	repetition time
TSE	turbo spin-echo
WE	water excitation

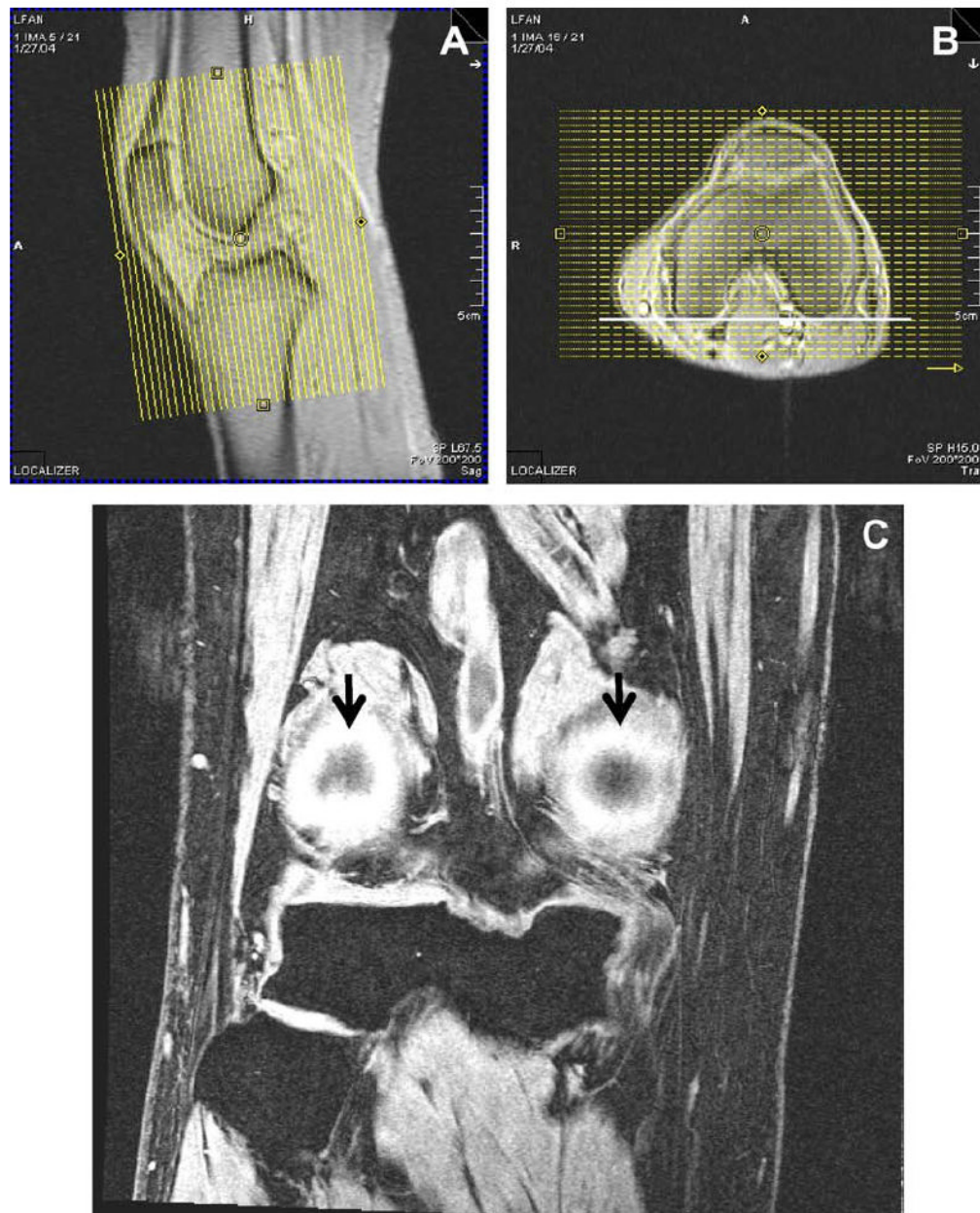


Fig. 1. Orientation of coronal acquisitions. Coronal 2D and 3D acquisitions are prescribed coronal to the joint, with the slice axis parallel to the long axis of the femoral diaphysis on the sagittal localizer (A) and to a line tangent to the posterior cortices of the femoral condyles on the axial localizer (B). Depiction of both posterior femoral cortices (arrows) within two slices (3 mm) of each other confirms proper alignment on this example of COR 3D FLASH WE (C).



Fig. 2. Example of COR IW 2D TSE. Note delineation of the MCL, LCL, body segments of the menisci, central tibial and femoral bone margins and the central tibiofemoral articular cartilage. Note that chemical-shift artifact is relatively mild.

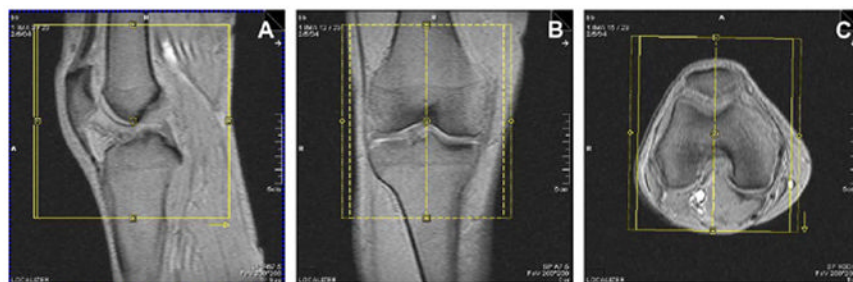


Fig. 3. Orientation of the sagittal acquisitions. Anatomical coverage on sagittal 2D and 3D acquisitions should include the tibial tubercle, the entire patella and as much of the suprapatellar bursa as possible (A) Sagittal acquisitions are prescribed orthogonal to the coronal acquisitions and sagittal to the joint, with the slice axis parallel to the long axis of the femoral diaphysis on the coronal localizer (B) and perpendicular to a line tangent to the posterior cortices of the femoral condyles on the axial localizer (C).

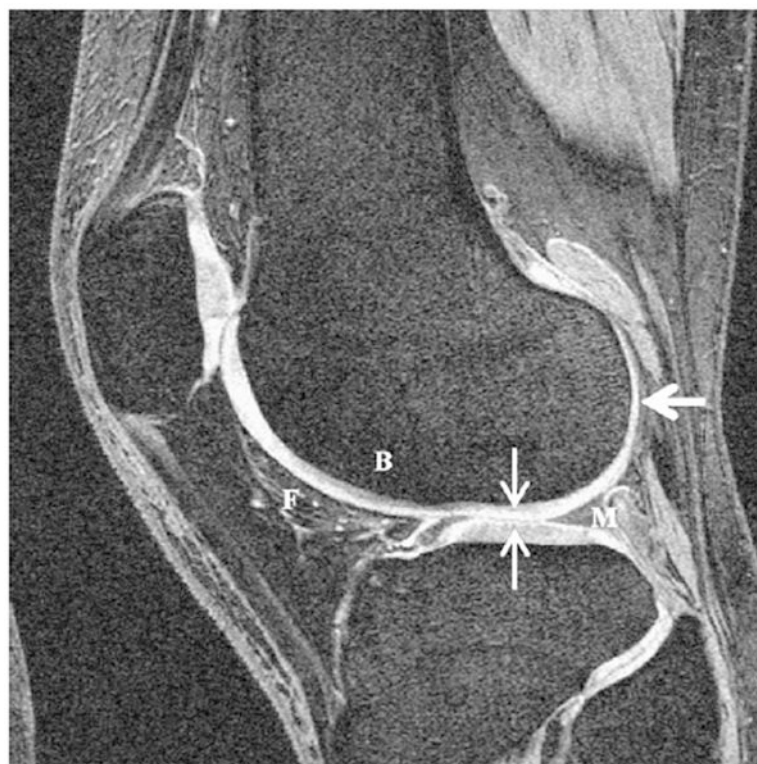


Fig. 4. SAG 3D DESS WE. Note the clear delineation of the cartilage-cartilage (small arrows) and cartilage-capsule (large arrow) interfaces as well as the interfaces between cartilage and adipose (F), bone (B) and meniscus (M).

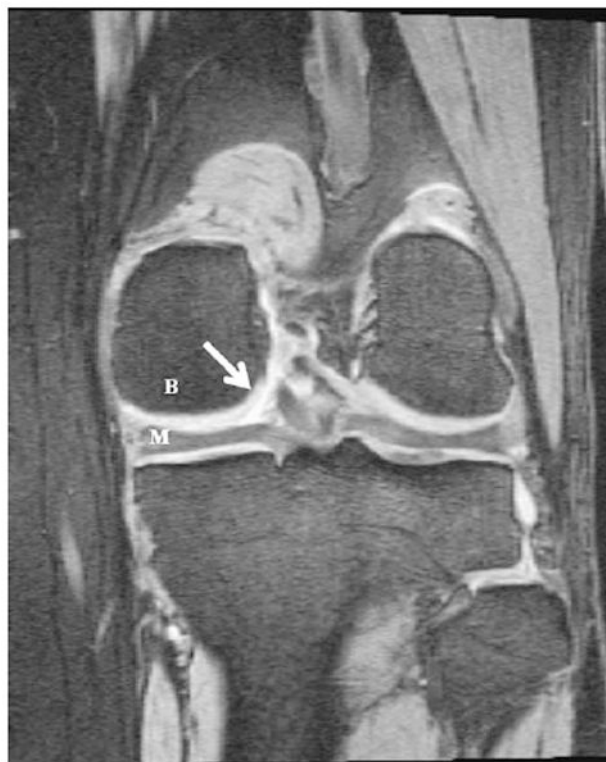


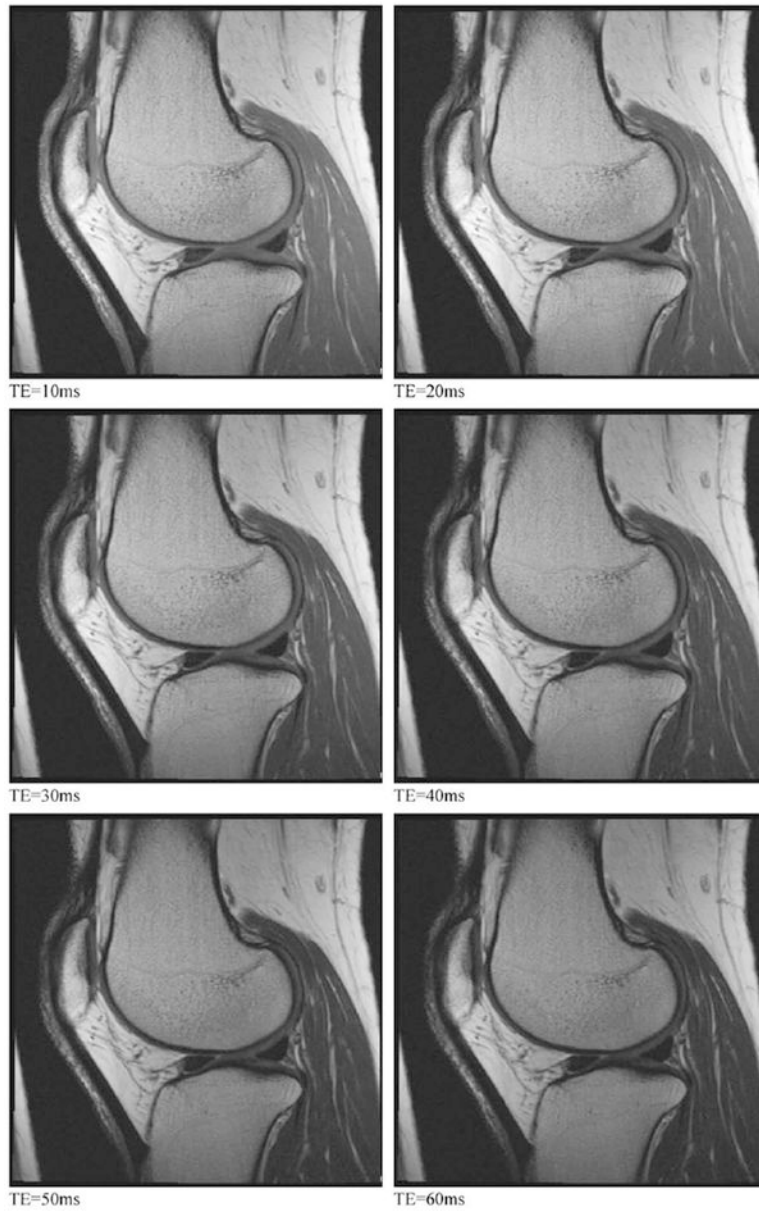
Fig. 5. Coronal MPR of SAG 3D DESS WE. Orientation is identical to that described in Fig. 1. Note the excellent delineation of the cartilage–fluid interface (arrow), and the high contrast between cartilage and bone (B) and cartilage and meniscus (M).

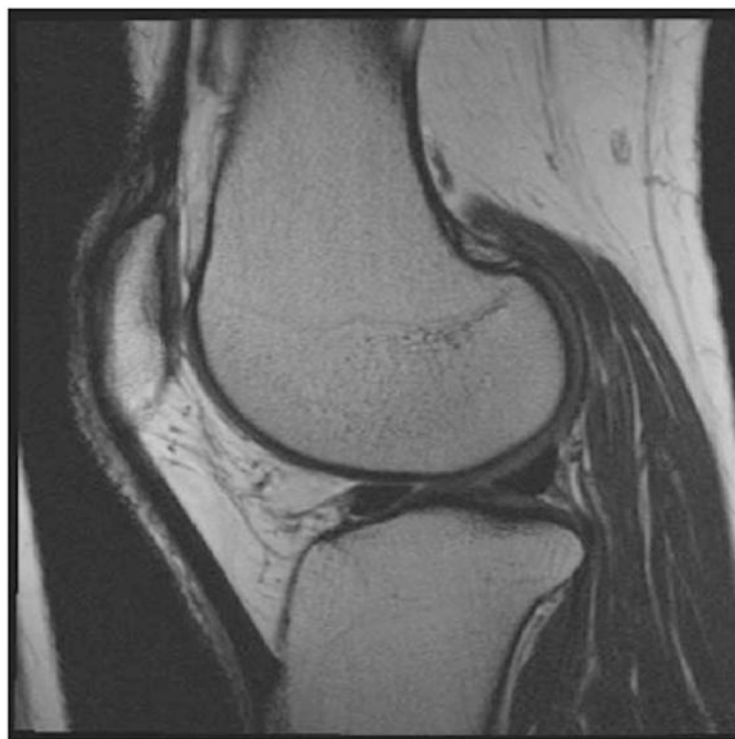


Fig. 6. Axial MPR of SAG 3D DESS WE. Axial coverage includes any superior or inferior patellar osteophytes and extends to the tibial epiphysis. Note the good cartilage–fluid contrast revealing thinning of articular cartilage over the lateral facet of the patella (large arrow). Note also, that a small aliasing artifact (small arrow) is present at the top of the image but does not obscure any anatomy of interest.



Fig. 7. Sensitivity to subarticular BMA and cysts. SAG IW 2D TSE FS (A) shows both bone cysts (small arrow) and surrounding BMA (large arrow) in the femoral trochlea of this knee. However, both GRE scans, SAG 3D DESS WE (B) and COR 3D FLASH WE (C), of the same knee show only the cysts in this location.





TE=70ms

Fig. 8. SAG 2D MESE. Multiple contrast acquisitions having progressively longer TEs can be combined to generate T2 maps of the articular cartilage and adjacent tissues. These seven images illustrate how changing the TE affects the relative signal and relative contrast among the different tissues in the knee.

Table I

Final OAI knee MRI protocol acquisition time (min)

	Scan	Right knee	Left knee	Total
1	Localizer (3-plane)	0.5	0.5	1.0
2	COR IW 2D TSE	3.4	3.4	6.8
3	SAG 3D DESS WE	10.6	10.6	21.2
4	COR MPR SAG 3D DESS WE	0.0	0.0	0.0
5	AXIAL MPR SAG 3D DESS WE	0.0	0.0	0.0
6	COR T1W 3D FLASH WE*	8.6	–	8.6
7	SAG IW 2D TSE FS	4.7	4.7	9.4
8	SAG 2D MESE*	10.6	–	10.6
	Total	38.4	19.2	57.6

* Acquired on only right knee, unless right knee contains metal in which case, acquired on only left knee.

Table II

Final OAI knee MRI protocol acquisition parameters

Scan	Localizer	COR IW 2D TSE	SAG 3D DESS WE	COR TIW 3D FLASH WE	SAG 2D MESE	SAG IW 2D TSE FS
Plane	3-plane	Coronal	Sagittal	Coronal	Sagittal	Sagittal
FS	No	No	WE	WE	No	FS
Matrix (phase)	128	307	307	512	269	313
Matrix (frequency)	256	384	384	512	384	448
No. of slices	21	35	160	80	21	37
FOV (mm)	200	140	140	160	120	160
Slice thickness/gap (mm/mm)	5/1	3/0	0.7/0	1.5/0	3/0.5	3/0
Flip angle (°)	40	180	25	12	n/a	180
TE/TR (ms/ms)	5/10	29/3700	4.7/16.3	7.57/20	10, 20, 30, 40, 50, 60, 70/2700	30/3200
Bandwidth (Hz/pixel)	250	352	185	130	250	248
Chemical shift (pixels)	1.8	1.3	0	0	1.8	0
No. excitations averaged	1	1	1	1	1	1
ETL	1	7	1	1	1	5
Phase encode axis	A/P, R/L	R/L	A/P	R/L	A/P	A/P
Distance factor (%)	50	0	0	0	16	0
Phase oversampling	0	20	0	0	0	40
Slice oversampling	0	0	10	0	0	0
Phase resolution	50	80	80	100	70	70
Phase partial Fourier (8/8 = 1)	1	1	1	1	0.875	1
Readout partial Fourier (8/8 = 1)	1	1	1	1	1	1
Slice partial Fourier (8/8 = 1)	1	1	0.75	0.75	0.75	1
X-resolution (mm)	0.391	0.365	0.365	0.313	0.313	0.357
Y-resolution (mm)	0.781	0.456	0.456	0.313	0.446	0.511