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MRI-based extended ordered values more efficiently differentiate cartilage loss in knees with and without joint space narrowing than region-specific approaches using MRI or radiography — data from the OA initiative

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SUMMARY

Objective: The sensitivity to change of quantitative analysis of cartilage in knee osteoarthritis using magnetic resonance imaging (MRI) is compromised by the spatial heterogeneity of cartilage loss. We explore whether extended (medial–lateral) "ordered values" (OVs) are superior to conventional approaches of analyzing subregional cartilage thickness loss and to radiography, in differentiating rates of progression in knees with and without joint space narrowing (JSN).
Methods: 607 Osteoarthritis Initiative (OAI) participants (308 without and 299 with baseline JSN at baseline) were studied over 12 months. Subregional femorotibial cartilage loss was determined in all knees, and changes in minimum joint space width (mJSW) in a subset of 290 knees. Subregional thickness changes in medial and lateral tibial and femoral cartilages were sorted in ascending order (OV1-16). A Wilcoxon rank-sum test was used to compare rates of change in knees with and without JSN.
Results: JSN-knees displayed greater cartilage loss than those without JSN, with minimal *P*-values of 0.008 for femorotibial subregions, 3.3×10^{-4} for medial OV1, and 5.4×10^{-7} for extended (medial and lateral) OV1. mJSW measurements ($n = 290$) did not discriminate between longitudinal rates of change in JSN vs no-JSN knees ($P = 0.386$), whereas medial OV1 ($P = 5.1 \times 10^{-4}$) and extended OV1 did ($P = 2.1 \times 10^{-5}$).
Conclusion: Extended OVs showed higher sensitivity to detecting differences in longitudinal rates of cartilage loss in knees with and without baseline JSN than anatomical (sub)regions and radiography. The OV technique also circumvents challenges of selecting particular regions "a priori" in clinical trials and may thus provide a powerful tool in studying risk factors or treatment efficacy in osteoarthritis.

Introduction

Quantitative MRI has emerged as a powerful tool for elucidating the natural progression and patho-physiology of osteoarthritis (OA), for identifying risk factors of OA, and for evaluating the effect of structure or disease modifying OA drugs (DMOADs)[1–4]. However, recent studies employing MRI technology reported that

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longitudinal changes of cartilage thickness in OA displayed a great amount of spatial heterogeneity between femorotibial joint compartments (medial, lateral), plates (tibia, femur), and subregions[5–12]. Previous studies hypothesized that cartilage loss in knee OA may preferentially occur in certain subregions of the femorotibial joint[5,13], but recent evidence suggests that the MRI-based sensitivity to change for anatomically defined subregions is not relevantly improved when compared to the analysis of total cartilage plates: Although central femorotibial subregions generally displayed greater rates of change than peripheral ones[5,10], the intersubject variability of central changes was also higher than for total cartilage plates[6,10]. Potential explanations for this observation are that only some knees show preferential central changes, and that once the cartilage is lost centrally, no further progression can be observed in central subregions. Moreover, a recent study showed that local meniscus lesions (in the anterior or posterior horn or body) are associated with higher rates of progression in immediately adjacent tibial cartilage subregions[14]. The fact that meniscal lesions are frequent[15] and strongly related to OA progression[16,17] provides a potential explanation, why rates of cartilage loss display strong spatial heterogeneity in peripheral subregions in OA.

As a potential solution to this challenge, Buck et al.[18] recently proposed a strategy for more efficiently measuring cartilage loss in OA by removing the link between magnitudes and locations of regional thickness changes in MRI. The authors showed that determining OVs of subregional change within the MEDIAL femorotibial compartment of each knee (medial OV approach) and then ranking the subregional change according to its magnitude, provided improved discrimination of cartilage loss between changes in healthy subjects and participants with MEDIAL radiographic OA. However, in general OA populations, a problem arises from the fact that some knees show preferential changes in the medial and others in the lateral femorotibial compartment, partly caused by differences in limb alignment[17,19–22]. In clinical trials, this can be circumvented by only selecting knees with either medial or lateral disease but this substantially increases the effort and cost involved in participant selection and also limits generalizability. Moreover, a recent study investigating the potential structure modifying effects of licofelone and naproxen[23] selected patients with MEDIAL femorotibial radiographic change and defined the MEDIAL compartment cartilage volume changes as the primary efficacy outcome measure. Although the primary outcome was reached in this study, the protective effect of licofelone was more evident in the lateral than in the medial compartment.

The objectives of the current study were:

1) to extend the proposed OV approach[18] to not only include medial but also lateral femorotibial subregions, in order to account for knees with both medial and lateral (radiographic) OA
2) to apply this approach to the analysis of cartilage thickness changes (i.e., cartilage loss) as a measure of OA progression in a large subset of knees with and without radiographic JSN at baseline, provided by the OAI[9,24–26].
3) to examine whether the extended OV approach shows a greater statistical sensitivity to differences in longitudinal cartilage changes between knees with and without baseline JSN than
   a) the medial OV approach,
   b) the region-based approach, and
   c) the mJSW approach, using radiography.
4) to further explore the statistical specificity of the extended OVs approach in relation to the region-based approach and the medial OVs approach.

Methods

Study participants

The study was based on the analysis of right knees from the OAI (public use data sets 0.2.2 [baseline clinical], 0.E.1 [baseline images], and 1.E.1 [12 month follow-up images]) and was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with local Institutional Review Board, informed consent regulations, and International Conference on Harmonization Good Clinical Practices Guidelines. Knees were randomly selected based on (1) ascending OAI ID and (2) the "calculated" Kellgren and Lawrence grades (cKLG), derived from osteophyte and radiographic JSN readings performed at baseline at the OAI clinical sites, according to the Osteoarthritis Research Society International (OARSI) atlas[27]. For the current study, we selected 607 knees with definite osteophytes and with either moderate JSN (299 knees with Osteoarthritis Research Society International (OARSI) grade 1 or 2:113 males, 186 females)[27] or without JSN at baseline (308 knees: 111 men, 197 females), because previous studies have shown a higher rate of cartilage thickness changes in knees with advanced radiographic OA (i.e., with baseline JSN) than in knees with less advanced radiographic OA (i.e., without baseline JSN)[7,8,28,29]. In this context it is worth noticing that although JSN is clearly associated with cartilage thickness loss[30], there is substantial variability between OA participants, and JSN is additionally influenced by meniscus extrusion and degeneration[31].

For 290 of the above knees, longitudinal (quantitative) measurements of medial minimum joint space width (mJSW)[32] have recently been made available by the OAI (J Duryea, Brigham and Womens Hospital, Boston, MA, USA) based on fixed flexion radiographs[33] obtained at baseline and at 12 month follow-up. From these 147 displayed baseline JSN in site readings and 143 did not.

MR image analysis

Double oblique, coronal MR images were acquired at baseline and 12 month follow-up, using a fast low angle shot sequence with water excitation (FLASHwe), 3 Tesla MR scanners (Siemens Magnetom Trio, Erlangen, Germany) and quadrature transmit-receive knee coils (USA Instruments, Aurora, OH, USA); the imaging protocol and quality control procedures have been described in detail in previous publications[9,24,25,34] (Fig. 1). After a quality control step (MH) at the image analysis center (Chondrometrics GmbH, Ainring, Germany), the data were analyzed by seven readers, each with more than 3 years experience in cartilage segmentation. The segmentation was performed for paired baseline and 12 month follow-up images, the readers being blinded to the order of the acquisition as well as to the clinical and radiographic data. The subchondral bone area (tAB) and the cartilage surface area (AC) were traced manually in the medial (MT) and lateral tibia (LT) and in the central, weight-bearing part of the medial femoral condyle (cMF) and central, weight-bearing part of the lateral femoral condyle (cLF). All segmentations were quality controlled by an expert reader (SM) and were corrected by the readers, if necessary. The mean cartilage thickness over the total subchondral bone area, including denuded areas, (ThCtAB) was determined in cartilage plates (MT, LT, cMF and cLF) and compartments (medial femorotibial compartment = MFTC = MT + cMF and lateral femorotibial compartment = LFTC = LT + cLF). Subregional thickness was determined in the central, external, internal, anterior, and posterior aspect of MT and LT, and in the central, external, and internal aspects of cMF and cLF, as described previously[13] (Fig. 1). The central subregions were set to cover 20% of the tAB in MT and LT, and 33% in cMF and cLF.
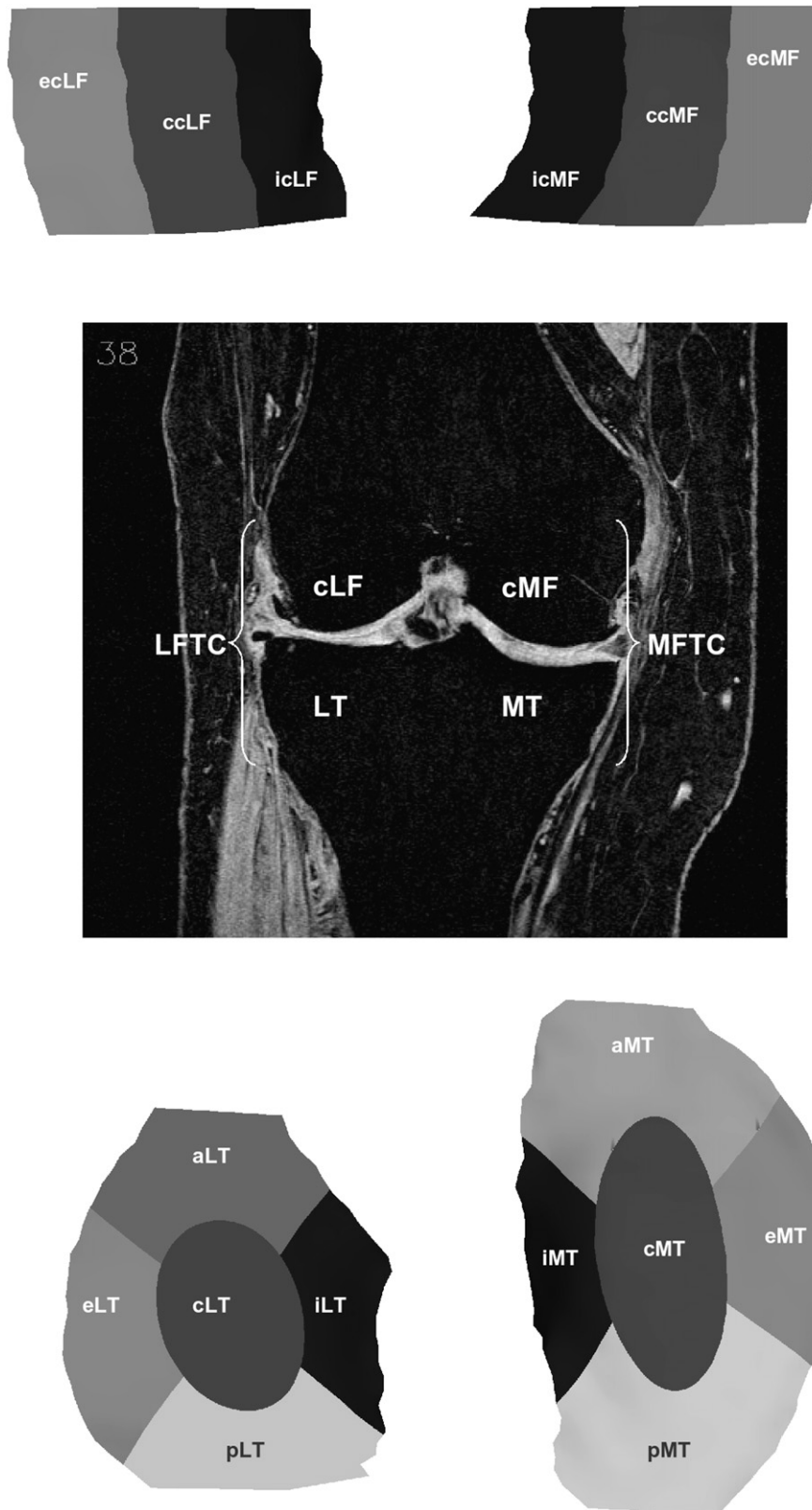
Fig. 1. Double oblique coronal fast low angle shot (FLASH) MR image with water excitation showing the regions of interest analyzed: MFTC (=MT + cMF), LFTC (=LT + cLF). The top part of the figures shows a reconstruction of the weight-bearing parts of the femoral condyles (cMF and cLF) and the lower part a reconstruction of the tibiae (MT and LT). (c|e|i|a|p = central|external|internal|anterior|posterior subregion of MT or LT. c|e|i = central|external|internal subregion of the central part of cMF or cLF).

Statistical analysis

Differences in subject characteristics between subjects with and without baseline JSN were assessed using two-sided *t*-tests. All longitudinal analyses including only MRI data were applied to the full cohort ($n = 607$), whereas the comparison between longitudinal MRI and radiographic mJSW were performed for the subcohort ($n = 290$). As a measure of progression, the mean change (MC) and the standard deviation (SD) of the change in μm for ThCtAB (MRI) and mJSW (radiography) between baseline and 12 month follow-up were determined. Percent changes were derived by relating the MC observed across a group to the respective average baseline value. The differences between the changes in the compared groups were described by the mean difference and 95% confidence intervals. The OV approach[18] was extended to comprise all 16 subregions in the femorotibial joint (five in MT and LT, and three in cMF and cLF, respectively): Subregional changes (in ThCtAB) within each knee were sorted in ascending order, i.e., the subregion showing the most negative change (decrease in ThCtAB) was assigned to extended ordered value (eOV) 1, and the value of the subregion showing the smallest negative or greatest positive change (increase in ThCtAB) was assigned to eOV 16 (Fig. 2).

To compare the rates of progression (cartilage thickness loss) in no-JSN and JSN knees, the MC and SD were evaluated for each compartment, cartilage plate and subregion as well as for the medial (mOV) and eOV approach (medial and lateral) (mOV 1–8, and eOV 1–16, respectively). The non-parametric Wilcoxon rank-sum test was used to determine whether the changes differed significantly between the JSN and the no-JSN knees, because the longitudinal changes may not be normally distributed.

Because the chance of at least one type I error increases with the number of parallel comparisons, and because the number of parallel comparisons differed between compartments (two measures), cartilage plates (four measures), subregions (16 measures), and OVs (eight measures for mOVs, 16 measures for eOVs), the individual test significance levels were adjusted for the number of (parallel) comparisons (Bonferroni–Dunn correction for overall significance level = 0.05): $P < 0.025$ for two compartments; $P < 0.0125$ for four plates, $P < 0.003125$ for 16 subregions,

$P < 0.00625$ for eight mOVs and $P < 0.003125$ for 16 eOVs. The significance levels were adjusted within each hierarchical category of joint compartments ($n = 2$), cartilage plates ($n = 4$) or cartilage subregions ($n = 16$), but not across these categories, because lower hierarchical levels are contained in (and correlated with) higher levels.

To further explore the statistical sensitivity of the different MRI-measures, the bootstrapping approach[35] was employed to simulate 10,000 "new" samples derived from the original study cohort by sampling the observed changes with replacement. The sample sizes (no-JSN and JSN) were kept constant.

The specificity of all measures is theoretically fixed during the testing procedure, as it corresponds to the level of false positives (significance level α), which is stated a priori. This is a theoretical assumption, however, and it is worthwhile to assess whether new testing procedures match the desired significance level. A randomization test assigning the observed changes in the JSN cohort for 10,000 times randomly without replacement to two subcohorts was employed for this purpose. For both the boot-strapping and the randomization method, the percentage of *P*-values below the unadjusted and the adjusted level of significance, and the median and SD of *P*-values were determined using the Wilcoxon rank-sum test, to assess the test characteristics of power (sensitivity) and significance level (specificity) for each measure.

Results

The no-JSN participants displayed a marginally lower age (60.6 ± 9.0 vs 64.2 ± 9.4 years, $P = 7.5E^{-6}$), body height (166.3 ± 8.7 cm vs 168.2 ± 9.4 cm; $P = 0.014$), and body weight (81.6 ± 15.2 kg vs 84.4 ± 16.8 kg; $P = 0.022$) than the JSN partici-pants. The difference in BMI (29.4 ± 4.6 kg/m^2 vs 29.8 ± 4.7 kg/m^2), however, was not statistically significant ($P = 0.199$). In the sub-cohort with both MRI and JSW readings ($n = 290$), age was signif-icantly different between knees with baseline JSN vs no-JSN ($P = 0.013$), but there were no significant differences in height ($P = 0.10$), weight ($P = 0.16$), and BMI ($P = 0.56$) between JSN and no-JSN knees.

A

OAI ID	cMT	eMT	iMT	aMT	pMT	ccMF	ecMF	icMF	cLT	eLT	iLT	aLT	pLT	ccLF	ecLF	icLF
9100262	-0.18	-0.25	0.08	-0.04	-0.21	-0.85	-0.72	-0.06	-0.10	0.04	-0.12	-0.04	0.02	0.01	0.04	-0.02
9135752	-0.25	-0.07	0.01	-0.12	-0.01	0.14	-0.09	0.03	-0.30	0.02	-0.08	0.06	-0.03	0.10	0.06	-0.09
9474248	-0.30	-0.02	-0.14	0.10	-0.01	-0.11	-0.13	-0.01	-0.62	-0.36	-0.18	-0.25	-0.11	-0.29	-0.38	-0.01
9725081	-0.12	-0.05	-0.01	-0.06	-0.01	-0.23	-0.15	-0.14	0.18	0.00	0.11	0.17	-0.34	-0.24	-0.04	-0.12
MC [μm]	-0.21	-0.10	-0.01	-0.03	-0.06	-0.26	-0.27	-0.05	-0.21	-0.07	-0.07	-0.01	-0.12	-0.10	-0.08	-0.06
SD [μm]	0.08	0.10	0.09	0.09	0.10	0.42	0.30	0.07	0.34	0.19	0.12	0.18	0.16	0.19	0.21	0.05

B

OAI ID	cMT	eMT	iMT	aMT	pMT	ccMF	ecMF	icMF	cLT	eLT	iLT	aLT	pLT	ccLF	ecLF	icLF
9100262	5	3	16	9	4	1	2	8	7	14	6	10	13	12	15	11
9135752	2	7	10	3	9	16	5	12	1	11	6	14	8	15	13	4
9474248	4	12	8	16	14	11	9	13	1	3	7	6	10	5	2	15
9725081	6	9	12	8	11	3	4	5	16	13	14	15	1	2	10	7

C

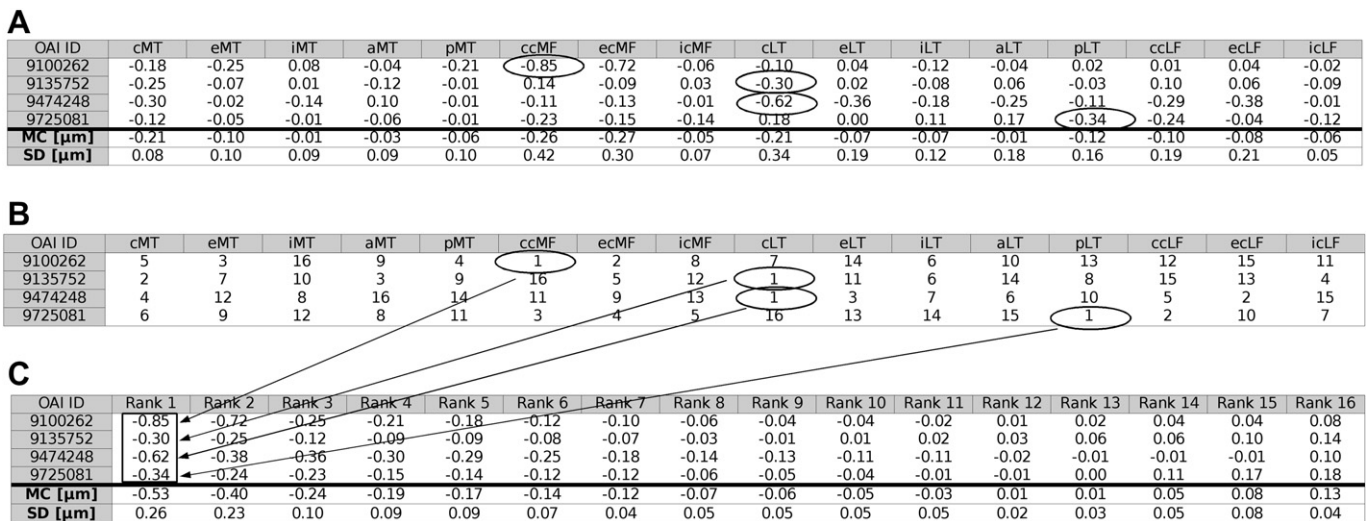| OAI ID	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11	Rank 12	Rank 13	Rank 14	Rank 15	Rank 16
9100262	-0.85	-0.72	-0.25	-0.21	-0.18	-0.12	-0.10	-0.06	-0.04	-0.04	-0.02	0.01	0.02	0.04	0.04	0.08
9135752	-0.30	-0.25	-0.12	-0.09	-0.09	-0.08	-0.07	-0.03	-0.01	0.01	0.02	0.03	0.06	0.06	0.10	0.14
9474248	-0.62	-0.38	-0.36	-0.30	-0.29	-0.25	-0.18	-0.14	-0.13	-0.11	-0.11	-0.02	-0.01	-0.01	-0.01	0.10
9725081	-0.34	-0.24	-0.23	-0.15	-0.14	-0.12	-0.12	-0.06	-0.05	-0.04	-0.01	-0.01	0.00	0.11	0.17	0.18
MC [μm]	-0.53	-0.40	-0.24	-0.19	-0.17	-0.14	-0.12	-0.07	-0.06	-0.05	-0.03	0.01	0.01	0.05	0.08	0.13
SD [μm]	0.26	0.23	0.10	0.09	0.09	0.07	0.04	0.05	0.05	0.05	0.05	0.02	0.03	0.05	0.08	0.04

Fig. 2. Graph showing the OVs approach: (A) The top spread sheet shows the results (change in cartilage thickness [ThCtAB] in μm) in the femorotibial subregions (see Fig. 1) of four example OAI subjects. (B) The rates of change are ranked according to their magnitude in the middle spread sheet. (C) The magnitudes of the changes (in μm) are then attributed to the orders in the bottom spread sheet. The subregion with the most negative change (decrease in ThCtAB) in each subject is assigned to order one, the subregion showing the second most negative change assigned to order two, and the subregion showing the smallest negative or the greatest positive change (increase in ThCtAB) assigned to order 16. Note that differently located subregions contribute to order one in the four subjects shown.

Table I
Femorotibial compartments and cartilage plates: change in cartilage thickness (ThCtAB) over 12 months in knees without baseline JSN (no-JSN, $n = 308$) and with baseline JSN (JSN, $n = 299$)

	no-JSN			JSN			Between-group		P-value	SL
	MC [µm]	SD [µm]	MC [%]	MC [µm]	SD [µm]	MC [%]	DIFF [µm]	CI [µm]		
MFTC	−12	100	−0.3	−40	128	−1.2	28	10/46	0.003*	0.025
LFTC	−8	81	−0.2	−29	126	−0.8	21	4/38	0.090	0.025
MT	−2	46	−0.1	−10	55	−0.6	8	0/16	0.027	0.013
cMF	−11	76	−0.6	−30	96	−1.8	20	6/33	0.007*	0.013
LT	−10	48	−0.5	−21	70	−1.1	11	1/20	0.119	0.013
cLF	2	58	0.1	−7	84	−0.4	10	−2/21	0.201	0.013

MC in µm or %, DIFF = mean difference between changes, CI = 95% confidence intervals of differences between changes (lower/upper limit), SL = significance level after Bonferroni−Dunn correction: The significance (P-value) of the differences between changes in JSN and no-JSN knees was computed using non-parametric Wilcoxon rank-sum tests and is reported in the table without adjustment for multiple comparisons. Compartments and cartilage plates showing significant differences after Bonferroni−Dunn correction ($P < 0.025$ for compartments, $P < 0.0125$ for cartilage plates) are marked with *.

In the total cohort ($n = 607$), the rate of change in the femorotibial compartments varied from −0.1% in LFTC of no-JSN knees to −1.2% in MFTC in JSN knees (Table I). The level of statistical significance of the differences in progression between no-JSN and JSN knees was higher for MFTC ($P = 0.003$ without correction for multiple testing) than for LFTC ($P = 0.090$). When analyzing cartilage plates, the rates of change (Table I) were greater for the femur than for the tibia medially, but were greater for the tibia than for the femur laterally (Table I). Differences in cartilage thickness loss between JSN vs no-JSN knees were most apparent in the medial femur (cMF; $P = 0.007$ without correction; Table I).

When analyzing femorotibial subregions, the greatest MCs were observed in the central aspect of the weight-bearing femur medially (ccMF) and in the central aspect of the tibia laterally (cLT) (Table II). cLT was also the subregion to best discriminate the rate of change between no-JSN and JSN knees ($P = 0.016$ without correction) laterally, whereas the level of significance for cartilage thickness loss in JSN vs no-JSN knees in the medial compartment was higher for the external aspect of the weight-bearing femur (ecMF; $P = 0.008$), the external aspect of the tibia (eMT; $P = 0.009$) and the posterior aspect of the tibia (eMT; $P = 0.022$) than for ccMF ($P = 0.030$) (Table II). In all of the eight medial, and in 13 of the 16 total (medial and lateral) subregions, the rates of cartilage thickness loss were greater for JSN than for no-JSN knees (Table III).

When analyzing mOVs in the total cohort ($n = 607$, Table III), four showed negative changes (cartilage thinning or loss), and four positive changes (cartilage thickening) in the no-JSN knees, whereas five showed negative changes and three positive changes in the JSN knees. The most significant difference in the rate of cartilage change between no-JSN and JSN knees was observed in OV1 ($P = 3.29 \times 10^{-4}$). mOV1 through three attained smaller P-values than found for any anatomical subregion, cartilage plate, or compartment (Tables I–III).

With the extended (medial and lateral) approach, eight OVs showed negative changes and eight positive changes in no-JSN knees, whereas nine showed negative changes and seven positive changes in JSN knees (Table III). The most significant differences in the rate of cartilage change between JSN and no-JSN knees were again observed for OV1 ($P = 5.38 \times 10^{-7}$). eOVs 1 through 7 attained smaller P-values than found for any anatomical subregion, cartilage plate, or compartment (Tables I–III) and OV1 through OV6 for the extended approach displayed a smaller P-value than any OV for the medial approach. The frequency with which the subregions represented eOV1 was not uniformly distributed and ranged between 2.6% (eMT, pMT & ecMF) and 14.6% (cLT) in the no-JSN sample and between 1.7% (aMT) and 16.1% (ccMF) in the JSN sample.

When correcting the observed P-values for multiple parallel testing at the compartment (two compartments) or plate level (four plates), a significantly different rate of change between JSN and no-JSN knees was observed in MFTC and cMF. In the 16 subregions, none of the changes differed significantly between JSN and no-JSN knees after Bonferroni−Dunn correction. In contrast, three of the eight mOVs, and seven of the 16 eOVs differed significantly

Table II
Femorotibial subregions: change in cartilage thickness (ThCtAB) over 12 months in knees without baseline JSN (no-JSN, $n = 308$) and with baseline JSN (JSN, $n = 299$)

	no-JSN			JSN			Between-group		P-value	SL
	MC [µm]	SD [µm]	MC [%]	MC [µm]	SD [µm]	MC [%]	DIFF [µm]	CI [µm]		
cMT	−8	91	−0.3	−24	103	−1.0	16	0/31	0.042	0.003
eMT	−6	80	−0.4	−21	88	−1.6	15	1/28	0.009	0.003
iMT	−4	65	−0.2	−8	70	−0.4	4	−7/15	0.331	0.003
aMT	4	64	0.2	3	69	0.2	1	−10/11	0.775	0.003
pMT	1	57	0.1	−8	61	−0.5	9	0/18	0.022	0.003
ccMF	−23	122	−1.0	−49	150	−2.5	26	4/48	0.030	0.003
ecMF	−4	84	−0.2	−22	105	−1.7	19	4/34	0.008	0.003
icMF	−7	69	−0.4	−22	86	−1.2	15	2/27	0.031	0.003
cLT	−21	98	−0.7	−49	139	−1.8	28	9/47	0.016	0.003
eLT	−6	67	−0.3	−16	81	−1.1	11	−1/23	0.270	0.003
iLT	−16	70	−0.8	−29	100	−1.7	13	−1/27	0.220	0.003
aLT	0	61	0.0	−5	75	−0.3	5	−5/16	0.235	0.003
pLT	−11	91	−0.6	−11	105	−0.6	0	−16/16	0.715	0.003
ccLF	2	85	0.1	−14	127	−0.6	15	−2/33	0.123	0.003
ecLF	4	71	0.3	−6	90	−0.4	10	−3/23	0.279	0.003
icLF	0	69	0.0	−4	85	−0.3	5	−8/17	0.447	0.003

The significance (P-value) of the differences between changes in JSN and no-JSN knees was computed using non-parametric Wilcoxon rank-sum tests and is reported in the table without adjustment for multiple comparisons. None of the femorotibial subregions showed significant differences after Bonferroni−Dunn correction ($P < 0.0031$).

Table III
Femorotibial orders (OV approach): change in cartilage thickness (ThCtAB) over 12 months in knees without baseline JSN (no-JSN, $n = 308$) and with baseline JSN (JSN, $n = 299$)

	no-JSN			JSN			Between-group		P-value	SL
	MC [μm]	SD [μm]	MC [%]	MC [μm]	SD [μm]	MC [%]	DIFF [μm]	CI [μm]		
Medial approach										
mOV 1	−98	101	−5.0	−125	125	−7.0	28	9/46	$3.3E^{-4}$*	$6.3E^{-3}$
mOV 2	−62	80	−3.6	−78	85	−4.8	16	2/29	0.004*	$6.3E^{-3}$
mOV 3	−33	50	−1.9	−50	70	−3.0	17	7/27	0.001*	$6.3E^{-3}$
mOV 4	−13	45	−0.7	−26	60	−1.6	12	4/21	0.009	$6.3E^{-3}$
mOV 5	6	42	0.4	−4	52	−0.2	10	3/18	0.011	$6.3E^{-3}$
mOV 6	26	42	1.5	17	51	1.0	9	1/16	0.016	$6.3E^{-3}$
mOV 7	48	46	2.7	41	59	2.4	7	−1/16	0.032	$6.3E^{-3}$
mOV 8	81	52	4.5	76	65	4.5	5	−4/15	0.198	$6.3E^{-3}$
Extended approach:										
eOV 1	−136	104	−6.5	−181	144	−9.4	45	25/65	$5.4E^{-7}$*	$3.1E^{-3}$
eOV 2	−97	80	−5.3	−126	95	−7.3	29	15/43	$9.6E^{-7}$*	$3.1E^{-3}$
eOV 3	−69	50	−3.7	−95	78	−5.4	27	16/37	$5.7E^{-7}$*	$3.1E^{-3}$
eOV 4	−53	43	−2.8	−73	61	−4.2	20	12/29	$1.5E^{-5}$*	$3.1E^{-3}$
eOV 5	−40	40	−2.1	−57	55	−3.2	17	9/25	$9.5E^{-5}$*	$3.1E^{-3}$
eOV 6	−29	39	−1.5	−43	50	−2.5	15	8/22	$2.2E^{-4}$*	$3.1E^{-3}$
eOV 7	−19	37	−1.0	−31	45	−1.8	12	6/19	0.001	$3.1E^{-3}$
eOV 8	−9	35	−0.5	−19	43	−1.1	10	4/16	0.006	$3.1E^{-3}$
eOV 9	1	34	0.0	−7	42	−0.4	8	2/14	0.032	$3.1E^{-3}$
eOV 10	10	32	0.5	4	43	0.2	6	0/12	0.099	$3.1E^{-3}$
eOV 11	21	32	1.2	16	43	0.9	4	−2/10	0.340	$3.1E^{-3}$
eOV 12	31	31	1.7	28	43	1.7	3	−3/9	0.786	$3.1E^{-3}$
eOV 13	44	33	2.4	42	44	2.5	2	−4/8	0.721	$3.1E^{-3}$
eOV 14	59	37	3.2	61	48	3.5	−1	−8/5	0.369	$3.1E^{-3}$
eOV 15	79	43	4.2	81	55	4.7	−1	−9/6	0.557	$3.1E^{-3}$
eOV 16	112	55	5.8	116	71	6.5	−4	−14/6	0.505	$3.1E^{-3}$

The significance (p-value) of the differences between changes in JSN and no-JSN knees was computed using non-parametric Wilcoxon rank-sum tests and is reported in the table without adjustment for multiple comparisons. mOVs and eOVs showing significant differences after Bonferroni−Dunn correction ($P < 0.0063$ for medial, $P < 0.0031$ for eOVs) are marked with *. OVs were computed from subregional changes in 8 (medial approach)/16 (extended approach) subregions in the medial (medial approach)/medial and lateral (extended approach) femorotibial joint. OV 1 = subregion showing the most negative change (decrease in ThCtAB) in each subject, OV 2 = subregion showing the second most negative change, ...OV 8 (medial approach)/16 (extended approach) = subregion showing the smallest negative or the greatest positive change (increase in ThCtAB).

between JSN and no-JSN knees. None of the OVs with positive changes (cartilage thickening) displayed significant differences between JSN and no-JSN knees after Bonferroni−Dunn correction, both for the medial and for the extended approach.

In the subcohort of knees with quantitative measurement of the radiographic mJSW ($n = 290$), the rate of change in mJSW did not differ significantly ($P = 0.386$) between JSN and no-JSN knees (Table IV). mOV1 ($P = 5.12 \times 10^{-4}$) and the eOV1 ($P = 2.10 \times 10^{-5}$), however, significantly discriminated rates of progression between JSN and no-JSN knees even after Bonferroni−Dunn correction for multiple testing.

The percentage of P-values below the adjusted significance level of 0.05 was higher for the first five eOVs (range 80.1%−96.7%) than for any of the other measures (range 0.4%−77.6%), when comparing changes of JSN vs no-JSN knees using the bootstrapping method.

The distribution of P-values varied from unimodal distributions for parameters showing a high percentage of P-values below the significance level (e.g., eOV 1−3) to an approximate uniform distribution (e.g., aMT, see Table V & Fig. 3). The median P-value obtained from the within-group randomization (Table V) was between 0.49 and 0.51 with a SD of 0.29 for all measures. All distributions of P-values approximated the uniform distribution (see Table V & Fig. 3).

Discussion

In this study we tested the hypothesis that an eOVs approach is superior to conventional approaches of measuring subregional MRI-based cartilage thickness loss, and to radiography, in longitudinally differentiating rates of progression in knees with

Table IV
Change in minimal medial joint space width (mJSW), medial compartment cartilage thickness, and OVs of subregional cartilage thickness (ThCtAB) change over 12 months in knees without baseline JSN ($n = 143$) and with baseline JSN ($n = 147$) for which longitudinal mJSW and the MRI outcomes were available

	no-JSN			JSN			Between-group		P-value	SL
	MC [μm]	SD [μm]	MC [%]	MC [μm]	SD [μm]	MC [%]	DIFF [μm]	CI [μm]		
mJSW	−81	575	−1.7	−129	654	−3.3	48	−94/190	0.386	0.050
MFTC	−18	113	−0.5	−59	142	−1.7	41	11/70	0.007*	0.025
MT	−4	50	−0.2	−12	59	−0.7	8	−5/21	0.160	0.013
cMF	−14	83	−0.7	−47	110	−2.7	32	10/55	0.002*	0.013
mOV 1	−102	107	−5.1	−146	152	−8.2	43	13/74	$5.1E^{-4}$*	$6.3E^{-3}$
eOV 1	−140	110	−6.4	−198	169	−10.4	58	25/91	$2.1E^{-5}$*	$2.9E^{-3}$

The significance (P-value) of the differences between changes in JSN and no-JSN knees was computed using non-parametric Wilcoxon rank-sum tests and is reported in the table without adjustment for multiple comparisons. Parameters showing significant differences after Bonferroni−Dunn correction ($P < 0.025$ for compartments, $P < 0.0125$ for cartilage plates, $P < 0.0063$ for medial, and $P < 0.0031$ for eOVs) are marked with *. mOV1 = subregion showing the most negative change (decrease in ThCtAB) in the MFTC of each subject. eOV1 = subregion showing the most negative change (decrease in ThCtAB) in the medial or the lateral femorotibial compartment of each subject.

Table V
Percentage of P-values less than 0.05 computed using the bootstrapping method between knees without and with JSN and computed using a randomization of knees with JSN

	aSL	Bootstrap (no-JSN vs JSN knees)				Randomization (JSN knees)			
		% (P < SL)	% (P < aSL)	Median	SD	% (P < SL)	% (P < aSL)	Median	SD
Regional approach									
MFTC	0.0250	84.7	76.9	2.6E-03	0.09	4.9	2.6	0.50	0.29
LFTC	0.0250	34.8	25.4	0.11	0.27	4.9	2.4	0.50	0.29
MT	0.0125	60.4	39.4	0.03	0.19	4.8	1.2	0.50	0.29
cMF	0.0125	77.8	58.6	0.01	0.12	5.0	1.2	0.50	0.29
LT	0.0125	29.8	14.5	0.15	0.28	5.1	1.3	0.49	0.29
cLF	0.0125	22.9	10.6	0.22	0.29	4.7	1.1	0.50	0.29
cMT	0.0031	50.0	16.4	0.05	0.22	5.0	0.3	0.50	0.29
eMT	0.0031	75.0	37.6	0.01	0.13	4.8	0.3	0.50	0.29
iMT	0.0031	16.7	2.5	0.31	0.30	4.6	0.2	0.50	0.29
aMT	0.0031	5.8	0.4	0.49	0.29	4.9	0.3	0.50	0.29
pMT	0.0031	60.1	22.9	0.03	0.18	5.0	0.3	0.50	0.29
ccMF	0.0031	60.7	23.9	0.03	0.19	5.1	0.4	0.50	0.29
ecMF	0.0031	76.7	39.8	0.01	0.12	5.3	0.3	0.49	0.29
icMF	0.0031	59.0	22.3	0.03	0.20	4.9	0.2	0.51	0.29
cLT	0.0031	65.7	28.0	0.02	0.17	4.9	0.4	0.50	0.29
eLT	0.0031	17.7	2.7	0.28	0.30	4.9	0.4	0.50	0.29
iLT	0.0031	19.7	3.1	0.26	0.30	4.4	0.3	0.50	0.29
aLT	0.0031	23.3	4.3	0.21	0.29	5.5	0.4	0.50	0.29
pLT	0.0031	7.6	0.8	0.46	0.30	5.0	0.3	0.50	0.29
ccLF	0.0031	32.3	7.5	0.13	0.27	4.9	0.2	0.50	0.29
ecLF	0.0031	18.9	3.2	0.27	0.30	5.0	0.4	0.50	0.29
icLF	0.0031	10.7	1.2	0.40	0.30	4.6	0.3	0.51	0.29
mOVs									
mOV 1	0.0063	93.7	77.6	4.5E-04	0.05	5.1	0.6	0.50	0.29
mOV 2	0.0063	79.9	52.6	4.9E-03	0.11	5.1	0.6	0.50	0.29
mOV 3	0.0063	89.8	69.8	1.2E-03	0.07	5.3	0.6	0.50	0.29
mOV 4	0.0063	73.7	44.4	0.01	0.14	4.9	0.6	0.50	0.29
mOV 5	0.0063	73.1	43.9	0.01	0.14	4.9	0.7	0.50	0.29
mOV 6	0.0063	70.7	40.6	0.01	0.15	4.7	0.6	0.50	0.29
mOV 7	0.0063	61.9	31.9	0.02	0.18	4.8	0.6	0.49	0.29
mOV 8	0.0063	30.4	10.0	0.15	0.28	5.0	0.7	0.50	0.29
eOVs									
eOV 1	0.0031	99.8	96.7	1.9E-06	0.01	5.0	0.3	0.49	0.29
eOV 2	0.0031	99.7	96.2	2.2E-06	0.01	4.9	0.2	0.49	0.29
eOV 3	0.0031	99.9	97.4	1.0E-06	0.00	5.1	0.3	0.49	0.29
eOV 4	0.0031	98.9	90.0	2.1E-05	0.02	5.0	0.3	0.49	0.29
eOV 5	0.0031	96.7	80.1	1.4E-04	0.03	5.0	0.2	0.50	0.29
eOV 6	0.0031	94.8	74.0	3.1E-04	0.05	5.2	0.3	0.49	0.29
eOV 7	0.0031	90.2	62.2	1.1E-03	0.07	5.1	0.3	0.50	0.29
eOV 8	0.0031	75.3	38.5	0.01	0.13	5.2	0.4	0.50	0.29
eOV 9	0.0031	54.9	19.3	0.03	0.20	4.9	0.3	0.49	0.29
eOV 10	0.0031	36.5	8.8	0.10	0.27	5.1	0.3	0.50	0.29
eOV 11	0.0031	17.0	2.2	0.29	0.30	5.0	0.3	0.50	0.29
eOV 12	0.0031	6.1	0.4	0.47	0.29	5.0	0.3	0.50	0.29
eOV 13	0.0031	7.8	0.7	0.45	0.30	4.7	0.3	0.50	0.29
eOV 14	0.0031	10.8	1.4	0.39	0.30	5.0	0.3	0.51	0.29
eOV 15	0.0031	6.8	0.6	0.46	0.29	4.9	0.3	0.50	0.29
eOV 16	0.0031	7.6	0.7	0.45	0.30	4.8	0.3	0.50	0.29

SL = Significance level (0.0). aSL = Significance level (0.05) adjusted for multiple comparisons. % (P < SL) = Percentage of P-values less than the significance level. %(P < aSL) = Percentage of P-values less than the adjusted significance level (aSL). Median = Median P-value obtained from the P-values computed after each of the 10,000 bootstrapping runs (no-JSN vs JSN knees) and after each of the 10,000 randomization runs (JSN knees vs JSN knees). SD of the P-values. All P-values were computed using non-parametric Wilcoxon rank-sum tests. OVs were computed from subregional changes in 8 (medial approach: mOV 1−8)/16 (extended approach: eOV 1−16) subregions in the medial (medial approach)/medial and lateral (extended approach) femorotibial joint.

and without JSN at baseline. Because previous studies have suggested that knees with radiographic JSN at baseline display greater rates of cartilage loss than those without JSN[7,8,12], this hypothesis was tested in JSN vs no-JSN knees from the OAI. The primary purpose of the study was to explore the gain in sensitivity to differences between groups, when using the eOV approach to differentiate structural OA progression in two groups with previous evidence of differences in the rate of cartilage loss. It is important to note that this approach is not limited to the question of difference in cartilage loss of JSN vs no-JSN knees, but may also be applied to elucidate the impact of other risk factors on OA progression, or to evaluate the effect of a potential DMOAD.

The findings show that the removal of the link between the magnitude of change and its specific location (in any given knee) is highly effective in improving the sensitivity in detecting significant differences in the rates of progression between groups. Particularly in a cohort that includes knees with both medial and lateral radiographic OA (as in the current study), this may be attributed to the fact that changes occur only in some (but not in other) subregions, and that changes across different subregions (in the same or in the contralateral compartment) are not generally positively correlated. Radiography provides a composite measure of cartilage thickness, meniscus integrity and extrusion[31] and is unable to reveal the spatial heterogeneity of cartilage thickness changes, whereas MRI provides the
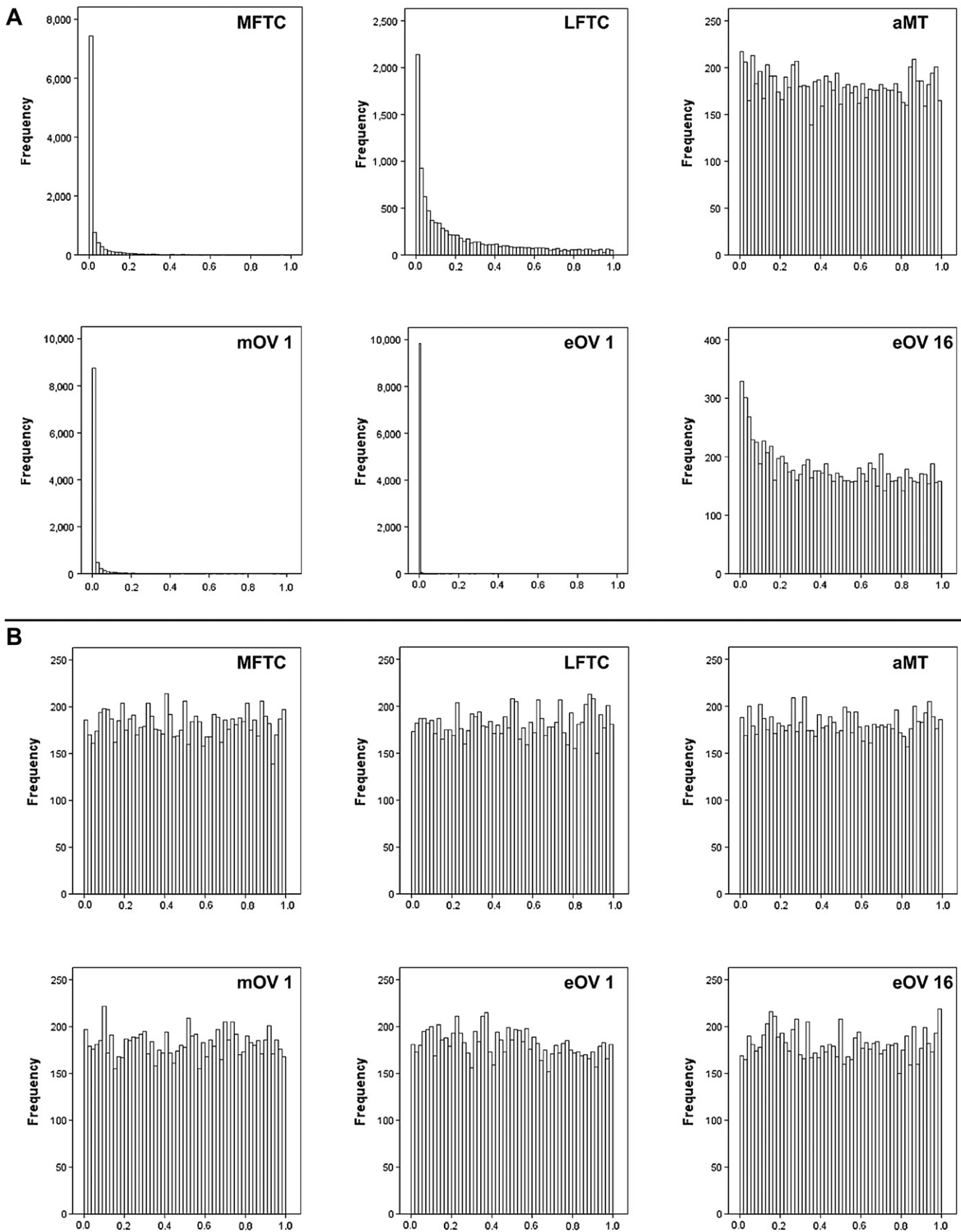
Fig. 3. Graphs showing the distribution of *P*-values obtained from (A) the bootstrapping method and from (B) the randomization of changes in JSN knees. The distribution is shown for the entire MFTC and LFTC, the anterior subregion of the medial tibia (aMT), the mOV1, and the eOV1, eOV16.

opportunity to capture change in multiple subregions. However, particular statistical approaches (i.e., OVs) are required, in order to fully exploit the value of subregional information that is provided. A potential downside of the eOV (medial and lateral) approach proposed is the need to perform segmentations in both femorotibial compartment, which extends analysis time and cost.

In the absence of an external gold standard, the results obtained with the bootstrapping method support the sensitivity levels observed for the different methodologies. The observed percentage of P-values below the defined significance level for the between-group differences was higher for the first five eOVs than for any other measure. This confirms the higher sensitivity to between-group differences for eOVs, even when adjusting for multiple comparisons.

The randomization of the changes within the group of JSN knees showed a similar specificity of all measures used in this study, as the P-values were almost uniformly distributed for all measured parameters and the median and SD observed for each parameter closely approximated the theoretical median (0.5) and SD (0.289) of a uniform distribution between 0 and 1. Because the number of false positives (percentage of P-values smaller than the significance level) was consistent with the defined false positive rate for all of the measures, the medial and the eOVs can be assumed to display a similar specificity as the regional approach.

A general challenge in designing a clinical trial in OA (either for identifying risk factors or for testing DMOADs) is to determine a primary outcome parameter (i.e., ThCtAB in a compartment, plate or subregion) "a priori". This is particularly true for MRI, which due to its three-dimensional nature allows for the analysis of changes (either quantitatively or semi-quantitatively) in a multitude of articular tissues, and also in a great number of anatomical subregions[36]. Previous studies employing quantitative (sub) regional cartilage analysis with MRI observed that longitudinal changes of cartilage thickness display substantial spatial heterogeneity between knees, and also found variable results between studies in reasonably sized cohorts[37]. Another recent study was unable to identify significant change in ThCtAB over relatively short observation periods of 3 and 6 months, despite the fact that the "most progressive" medial subregion (ccMF) was selected as an outcome, and albeit only knees with medial radiographic disease and several risk factors of OA progression were selected[38]. To overcome the limited sensitivity to change of quantitative MRI (and radiography) due to spatial heterogeneity of cartilage loss, Buck *et al.*[18] proposed an OV approach of subregional changes in MEDIAL compartment cartilage thickness. This approach used only the medial compartment because it was expected to be the region of greatest change in a study of subjects with medial disease, but within the medial compartment change may vary between knees[18], likely due to the individual mechanical and/or biological conditions. However, it is well known that, in general OA populations, knees preferentially show cartilage loss in the medial or lateral femorotibial compartment, and that limb alignment is the main determinant of medial vs lateral progression[17,19–22]. A recent DMOAD study comparing the sparing effects of licofelone and naproxen in OA defined loss of cartilage volume in the MEDIAL femorotibial compartment as the primary efficacy outcome measure[23]. Although this primary outcome measure was reached in this study, the authors reported the protective effect of licofelone to act predominantly in the LATERAL femorotibial compartment. The "extended" OV approach presented here can overcome this challenge in the context of clinical trials[23,38], as it does not require one to define the primary outcome "a priori" in terms of a specific compartment, cartilage plate or subregion. This not only permits

one to widen inclusion criteria during screening for a clinical trial (i.e., to include knees with either medial or lateral disease), but also to generalize the results by allowing one to examine a general OA cohort with few restrictions.

The results from the current study show that the spatial origin of OV1 is heterogeneously distributed across the joint, but that some subregions are more frequently involved (e.g., ccMF and cLT) than others (i.e., no random distribution). This heterogeneous distribution provides one of the reasons why OV1 is more sensitive to differences (in the rate of change) between groups than region-specific analyzes. The current study therefore shows for the first time that, when using an eOV approach, the level of sensitivity in differentiating rates of progression between JSN and no-JSN knees is substantially increased over radiography, the analysis of total cartilage plates and compartments, and the analysis of anatomically defined subregions. Additional statistical power may be gained when "a priori" defining OV1 alone as a primary outcome, or when averaging results over a group of orders (i.e., 1–4). Averaging changes in cartilage thickness for orders 1–4, however, did not provide lower P-values between JSN and no-JSN knees than OV1 alone (data not shown). The results of the current study thus indicate that, in context of baseline radiographic JSN, eOV1 is the most effective measure in determining differences in rates of cartilage loss. Further studies are required to determine whether this is also true for other risk factors of OA progression, or for treatment with specific DMOADs. If a DMOAD is primarily targeted at reducing cartilage loss, however, OV1 may potentially be used as an effective and powerful "single" outcome measure, whereas definition of a region-based outcome (compartment, plate or subregion) may involve greater needs (and costs) for selecting specific knees, and/or may increase the risk of study failure. Because of its potential for higher statistical power (both with and without correction for multiple testing), the OV approach may become a valuable tool for reducing the number of participants or the observation time in a clinical trial, without unnecessarily sacrificing the generality of the findings.

In conclusion, an eOV approach, based on medial and lateral femorotibial subregions, showed a higher discriminatory power than radiography, region-based approaches with MRI, and mOVs when comparing longitudinal cartilage thickness changes in knees with and without baseline JSN in knees from the OAI. Because the (extended) OV approach removes the link between the magnitude and location of change, it allows for the inclusion of knees with both medial and lateral disease, and of knees with different biomechanical risk factors influencing the load distribution within the femorotibial joint. As this circumvents the challenge of selecting a particular knee compartment or anatomical subregion as an outcome measure of progression "a priori", the approach may generally provide a powerful tool in studies targeting risk factor identification or treatment efficacy in OA.

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Competing interest statement

Wolfgang Wirth, Susanne Maschek and Martin Hudelmaier have part time appointments with Chondrometrics GmbH. Felix Eckstein is CEO of Chondrometrics GmbH, a company providing MR image analysis services. He provides consulting services to Pfizer, Merck Serono, Novo Nordisk, Wyeth, and Novartis. Marie-Pierre Hellio Le Graverand has a full time employment with Pfizer Inc., Olivier Benichou with Eli Lilly, Donatus Dreher with Merck Serono, Richard Y. Davies with GlaxoSmithKline, Jennifer Lee with Pfizer, Kristen Picha with Centocor, and Alberto Gimona with Novartis. Michael Nevitt has no competing interests.

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