Research Paper

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Brain gray matter abnormalities in osteoarthritis pain: a cross-sectional evaluation

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Abstract

The interaction between osteoarthritis (OA) pain and brain properties remains minimally understood, although anatomical and functional neuroimaging studies suggest that OA, similar to other chronic pain conditions, may impact as well as partly be determined by brain properties. Here, we studied brain gray matter (GM) properties in OA patients scheduled to undergo total joint replacement surgery. We tested the hypothesis that brain regional GM volume is distinct between hip OA (HOA) and knee OA (KOA) patients, relative to healthy controls and moreover, that these properties are related to OA pain. Voxel-based morphometry group contrasts showed lower anterior cingulate GM volume only in HOA. When we reoriented the brains (flipped) to examine the hemisphere contralateral to OA pain, precentral GM volume was lower in KOA and HOA, and 5 additional brain regions showed distortions between groups. These GM changes, however, did not reflect clinical parameters. Next, we subdivided the brain into larger regions, approximating Brodmann areas, and performed univariable and machine learning-based multivariable contrasts. The univariable analyses approximated voxel-based morphometry results. Our multivariable model distinguished between KOA and controls, was validated in a KOA hold-out sample, and generalized to HOA. The multivariable model in KOA, but not HOA, was related to neuropathic OA pain. These results were mapped into term space (using Neurosynth), providing a meta-analytic summary of brain anatomical distortions in OA. Our results indicate more subtle cortical anatomical differences in OA than previously reported and also emphasize the interaction between OA pain, namely its neuropathic component, and OA brain anatomy.

Keywords: Osteoarthritis, Chronic pain, Structural brain anomalies, Gray matter volume, VBM

1. Introduction

Osteoarthritis (OA) is the most common form of arthritis worldwide, one of the most prevalent sources of chronic musculoskeletal pain,[43] and a leading cause of disability.[14,42] Pain is the defining symptom and primary complaint of OA,[37] and its consequences include fatigue, sleep disruption, reduced activity, and psychological stress.[27] Understanding the mechanisms of pain in OA is thus critical for the management of the disease.

Traditionally, OA was considered the hallmark of nociceptive pain, explained by mechanical and biochemical activation of afferents innervating the affected joint.[29,63] Recent studies show evidence for peripheral sensitization of nociceptors[59] and central sensitization, associated with nociceptive-mediated transmission strengthening and dysfunction of descending modulator pathways in OA.[41] In addition, neuropathic-like symptoms,[19,28] negative affect, anxiety, and catastrophizing have been related with pain severity,[1,57] suggesting linkage between the brain's emotional circuitry and OA pain.

We[6,7,38,46] and other researchers[16,25,39] have provided evidence for brain anatomical and functional abnormalities in OA. Brain activity for ongoing OA pain[46] shows similar activity patterns as observed in chronic back pain (CBP).[6,26] Disruption of information sharing,[38] and brain morphological distortions are reported both in OA and in CBP.[7] Given that transition from subacute to CBP is predicted by brain anatomical and functional parameters[8,62] and chronification of back pain is accompanied by anatomical and functional reorganization,[26] a similar concept can be formulated for OA pain, namely, brain parameters in part predefine risk and consequently reorganize with OA pain. Here, we attempt to address this issue from the viewpoint of brain morphology. Hip OA (HOA) and knee OA (KOA) have distinct clinical characteristics, pain properties, and joint replacement surgery outcomes. For both conditions, pain is poorly related to joint structural damage.[18] Our main hypothesis is that KOA and HOA exhibit brain gray matter (GM) distortions when contrasted with healthy controls, and GM properties should also be different between the 2 conditions.

GM indices indicate morphologic brain abnormalities in OA,[2,25,34,39] but their clinical import is not yet understood. Although promising, these data are primarily derived from small samples at

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distinct stages of OA progression, and evidence is discrepant as GM changes exhibit little overlap between studies. Moreover, previous literature fails to find robust associations between clinical properties of OA and brain structural changes.[2,39] Our second objective is to study the association between brain morphological distortions and OA clinical properties.

We study brain morphological distortions and their relationship with clinical outcomes in a large population of advanced KOA, and a smaller group of HOA, in contrast to healthy controls. We study GM properties at whole-brain voxel-wise scale and after subdividing gray matter to regions of interest (ROIs) and apply both univariable and multivariable machine-learning analysis to explore the multidimensional basis of these alterations. Finally, we perform a reverse inference mapping of obtained results to terms (using Neurosynth), providing a meta-analytic summary of results and linking brain anatomy to the psychological domain.

2. Patients and methods

2.1. Subjects

Advanced HOA and KOA patients with indication for total joint replacement were recruited in the Orthopedic Department of *Centro Hospitalar e Universitário de São João*, Porto, together with healthy controls from the same geographical area. Participant recruitment was finished at the time of this report. Sample size was determined by the number of patients waiting for surgery who met the eligibility criteria during a period of 20 months. Controls were recruited in the end of the patient recruitment phase and intended to be one-third of the patient number in the largest OA group.

Inclusion criteria for OA patients were: (1) age between 45 and 75 years; (2) diagnosis of HOA and KOA according to the clinical classification criteria of the American College of Rheumatology[3]; (3) surgical indication for total joint replacement. Exclusion criteria included: (1) secondary OA due to congenital and development diseases or inflammatory and autoimmune articular diseases; (2) bilateral OA with indication for contralateral arthroplasty in the following year or bilateral knee pain with less than or equal to 4 points difference on the numeric pain rating scale between knees; (3) other chronic pain conditions (eg, fibromyalgia; chronic pelvic pain), (4) chronic neurological or psychiatric disease; (5) previous history of stroke or traumatic brain injury.

Controls were subjects without chronic conditions, musculoskeletal disorders, and neurological disorders, from the same geographic area, age range, and social and educational background as the patients.

Clinical, demographic, and biopsychosocial measures were obtained 2 to 6 weeks before surgery and repeated at 3, 6, and 12 months after surgery, together with brain imaging collection (magnetic resonance imaging [MRI]). The study was approved by the local ethics committee, and all participants provided informed consent before partaking in the study. In this article, we are reporting baseline cross-sectional data from presurgical state. Longitudinal data results will follow in future work.

2.2. Clinical and behavioral measures

Demographic and clinical data were obtained at the initial interview and by clinical chart assessment. Bilateral radiographs of involved joints were performed as part of the standard hospital protocol and scored accordingly to the Kellgren–Lawrence classification[32] by 2 trained radiologists. Physical performance was assessed with 2 distinct tasks—timed up and go test[47] and 6-minute walking test (6MWT).[9,50]

All patients completed the following questionnaires: Knee and Hip Injury and Osteoarthritis Score (KOOS; HOOS)[21,44,52]; Hospital Anxiety and Depression Scale (HADS)[45,67]; Pain Catastrophizing Scale[5,58]; and *Doleur Neuropathique en 4 questions*—Neuropathic pain scale (DN4).[5,12] All questionnaires were used in their Portuguese validated versions.

2.3. Brain imaging

High-resolution, MPRAGE type T1-anatomical brain images were acquired with a 3.0 T Siemens Magnetom Spectra scanner (Siemens Medical, Erlagen, Germany). Acquisition parameters: isometric voxel size = 1 × 1 × 1 mm, TR = 2500 ms, TE = 3.31 ms, flip angle = 9°, in-plane matrix resolution = 256 × 256, number of slices, = 160; field of view = 256 mm. Total time of acquisition was 6 minutes.

2.4. Gray matter properties and statistical analyses

GM properties were extracted, and analyses were performed using tools from the Oxford Center for Functional Magnetic Resonance Imaging Software Library (FMRIB, Oxford OK; FSL version 5.0.10, https://fsl.fmrib.ox.ac.uk/fsl)[31]; Matlab (MATLAB 2018a; The MathWorks, Natick, 2018), and RStudio (RStudio Team (2016); RStudio: Integrated Development for R. RStudio, Inc, Boston, MA URL http://www.rstudio.com).

2.4.1. Total gray matter volume estimation

SIENAx (2.6) from FSL[55,56] was used to calculate estimates of volumes of interest, after automated brain extraction and tissue segmentation. We compared total gray matter (GM) volume across groups using an analysis of covariance (ANCOVA), controlling for intracranial volume, age, and sex. Differential relationships between GM and age were assessed using linear regression, controlling for sex and total intracranial volume (TICV), in which a group interaction indicated a difference in slopes.

2.4.2. Voxel based morphometry

Regional GM density was analyzed with voxel-based morphometry (VBM) using tools from FSL. In brief, images were skull stripped using Brain Extraction Tool[55] and tissue-type segmented into GM, white matter, and cerebrospinal fluid using FMRIBs Automated Segmentation Tool.[66] A study-specific GM template was created using 72 gray-matter-segmented native images (24 subjects of each group; KOA and controls were randomly selected to minimize size of population bias). Steps towards the template creation included: affine registering the GM partial volume images (FLIRT)[30] and left-to-right x-axis flipping to produce a symmetrical image followed by nonlinear registration (FNIRT)[4] to standard space. The native space GM volume images were then normalized into this template using a nonlinear registration (FNIRT) and corrected for the contraction/enlargement due to the nonlinear component of the transformation using the Jacobian. Finally, GM images were concatenated and smoothed with an isotropic Gaussian kernel (FWHM = 8 mm). Cerebellum was excluded from the analyses because the foci of this study were neocortical and subcortical structures.

A second group for parallel VBM analysis was created by midline flipping the scans of patients with left-sided OA (knee = 45; hip = 10), in accordance with previous OA and unilateral pain conditions studies.[24,36] Brains were flipped along the x-axis

before nonlinear registration to the study template. All subsequent steps were identical.

Gray matter differences in OA groups and controls were assessed through a one-way between-subjects ANCOVA, using age, sex, and TICV, plus laterality of OA for the flipped data analysis as covariates of no interest. Permutation-based testing (n = 5000 permutations) was performed using FSL's randomize toolbox.[64] Threshold-free cluster enhanced uncorrected *P*-values were obtained,[54] and $\alpha = 0.001$ was used as threshold for statistical significance of group differences. A minimum cluster size of 66 voxels (number of voxels contained within the 8 mm smoothing kernel) was used as a secondary threshold. Post hoc analyses of VBM results using Tukey HSD tests for multiple comparisons of means were conducted for the identified clusters.

The association of significant clusters with clinical variables was examined using partial correlations, with age, sex, and TICV as covariates.

In addition to assessing simple group differences, we sought to understand their relationship with clinical variables. Thus, the association of significant clusters with clinical variables was examined using partial Pearson correlations, which controlled for age, sex, and TICV.

2.4.3. Regional Brodmann area parcellation-based analysis of gray matter GM morphometry volume

Next, we calculated GM volume for 90 cortical and subcortical ROIs approximating Brodmann areas, defined anatomically by the Automated Anatomical Labeling atlas (Neurofunctional Imaging Group [GIN-IMN] http://www.gin.cnrs.fr/en/tools/aal/).[61] Cerebellum and vermis areas were excluded from the analysis. A list of regions, labeling, and respective coordinates can be found in Table S1 (available online as supplemental digital content at http://links.lww.com/PAIN/B8).

The volume of each ROI was calculated as the mean GM volume of all voxels within the ROI for each subject. Volumes were calculated both for native brains and x-axis-flipped brains depending on laterality of OA. Univariable analyses were conducted using one-way ANCOVA test for each region contrasting the 3 groups: KOA, HOA, and controls, while controlling for age, sex, and TICV. For the flipped brain analysis, laterality was also added as a covariate. Again, an $\alpha = 0.001$ was used a threshold for statistical significance of group differences. Multiple comparison correction was performed using a false discovery rate-adjusted *P*-value of 0.05.

Next, a multidimensional approach using a L1-regularized logistic regression (ie, least absolute shrinkage and selection operator [LASSO])[60] was performed. First, we divided our KOA sample into 2 distinct sets, training (n = 46) and test (n = 45). This was performed using the Kennard–Stone algorithm,[33] which allowed us to select samples with a uniform distribution over a multivariate predictor space (here: age, sex, pain levels, and behavioral variables). Second, using the KOA training set, we performed a logistic model with a LASSO penalty to predict group membership (ie, knee vs controls), based on the GM volumes of all 90 ROIs. In addition, we added age, sex, and TICV to the full model. Ten-fold cross-validation was used to choose the hyperparameter, λ, which minimized binomial deviance over a default grid size of 100.[20] Finally, models were evaluated in the KOA test group and HOA group by constructing receiver operating characteristic curves and computing areas under the curve (AUC).

Later, Neurosynth term-based reverse inference was used to decode the identified AAL regions for the flipped brain model. This meta-analytical tool contains a database with activation coordinates for a total of 14,371 functional MRI studies (September 2019), paired with their associated cognitive and anatomical terms (http://neurosynth.org/decode/).[22,48,65] The decoder takes in the voxel-wise representation of the ROI, cross-references it with the full database, and returns a list of terms and correlation values, which indicates the strength of terms associated with delineated brain regions, in contrast to the rest of the brain. Here, we retrieved the top 40 nonanatomical terms (of about 1700 terms generated) showing the greatest correlation with the model's ROIs. Next, to further elucidate the contribution of each region in the model, the correlation for each ROI was weighted by its LASSO-derived coefficient and ranked. Terms were visualized using a word-cloud (MATLAB 2018a and Text Analytical Toolbox, The MathWorks, Natick, 2018).

Finally, we aimed to test whether the OA classification models were associated with OA clinical variables.

For this, using the KOA testing group, we linearly modeled each clinical variable of interest with the variables retrieved from the LASSO. For statistically significant relationships ($P < 0.05$), the relative importance of each independent variable was calculated using the sequential sums of squares over all orderings of regressors,[35] and confidence intervals computed over 1000 bootstraps for each regressor.[23] Finally, statistically significant regression models were tested in the KOA validation group and HOA group by calculating Pearson correlation coefficient between predicted and real values.

3. Results

3.1. Demographic and clinical characteristics

A total of 91 KOA patients, 24 HOA patients, and 36 healthy controls were included in the study. Patient and control groups were similar concerning education, habitation profile, marital status, and smoking habits. Age and sex were statistically significantly different among the 3 groups: age was higher in the KOA group and HOA had a lower representation of females.

Pain intensity as well as affective measures and performance-based tasks did not statistically significantly differ among OA groups. The KOA group, however, presented a longer pain duration and a higher probability of neuropathic pain than the HOA group, which in contrast exhibited higher radiographic structural damage (**Table 1**).

3.2. Total gray matter characterization

Total neocortical gray matter volumes (TGM) were compared between the 3 groups (OA and controls), while controlling for TICV, age, and sex. TGM was not statistically significantly different between the 3 groups ($F(2,145) = 0.07$, $P = 0.79$)). Women showed greater TGM than men (controlling for group, TIVC, and age) (**Fig. 1A**). The effect of age on TGM was calculated for each group separately (after correcting for sex). TGM decreased with age (**Fig. 1B**) and the interaction between age and group was not statistically significant ($F(2,145) = 2.62$, $P = 0.078$), showing approximately similar trends for the 3 groups.

3.3. Hip osteoarthritis patients exhibit lower GM volume in anterior cingulate/paracingulate cortex

To identify regional differences in GM volume between OA groups and controls, we performed a whole-brain, voxel-wise, one-way ANCOVA for VBM outcomes (**Fig. 1C**). Statistically significant differences in GM volume in the right and left anterior cingulate

Table 1

Demographic and clinical characteristics of osteoarthritis patients and controls.

	Controls		Knee OA		Hip OA		*P*
Subjects, n, %	36	23	91	60	24	16	
Age (y), mean, SD	59.2	8	65.5	6.5	59.7	8.2	<0.001†
Female, n, %	20	55.5	72	79.1	8	33.3	<0.001†
BMI (kg/m^2), mean, SD	27.8	4.6	30.4	4.9	28.3	3.7	0.06
Education, n, %							0.12
Primary education	21	58.3	71	78	16	66.7	
Secondary education	8	22.2	15	16.5	5	20.8	
Post-secondary education	7	19.5	5	4.5	3	12.5	
Smoking, n, %	8	22.2	8	8.8	2	8.3	0.09
Habitation, n, %							
Alone	6	16.7	17	18.7	3	12.5	
Cohabitation	30	83.3	74	81.3	21	87.5	
Marital status, n, %				6			0.9
Married	27	66.7	65	71.4	17	70.8	
Never married	3	8.3	5	5.5	2	8.3	
Divorced	2	5.6	7	7.7	2	8.3	
Widowed	4	11.1	14	15.4	3	12.5	
Pain duration (y), mean, SD	—	—	7.7	6	5.1	4.3	0.015*
Pain intensity (NRS), mean, SD	—	—	6.6	1.7	6	1.6	0.1
KOOS/HOOS, mean, SD	—	—	61.2	20	50.8	15	0.011*
Symptom	—	—	63.7	15.6	55.9	17.8	0.061
Pain ADL SR	—	—	62.6	16.4	58.8	18.1	0.354
QoL	—	—	91.9	13.9	83.6	18.6	0.049*
	—	—	79.5	15.3	71.1	20.3	0.061
HADS, mean, SD							0.354
Anxiety	—	—	8.8	5	6.8	4.4	0.061
Depression	—	—	7.1	4.1	6	4.6	0.354
PCS, mean, SD			8.3	4.8	7.5	4.	0.41
Rumination magnification	—	—	5	3.7	4.4	3.4	0.43
Helplessness	—	—	10	7.5	8.4	6.2	0.34
DN4, mean, SD	—	—	2.8	2.2	1.8	1.5	0.029*
Physical performance tasks, mean, SD							
TUG, seg	—	—	13.6	4.2	270.8	68.4	0.4
6MWT, meters	—	—	14.4	4.7	270.6	98.5	0.9
Radiographic KL, n, %							<0.001†
Grade 1	—	—	2	1.8	0	0	
Grade 2	—	—	21	23.1	0	0	
Grade 3	—	—	43	39.1	6	25	
Grade 4	—	—	25	22.8	18	75	

To identify demographic difference between groups, ANOVA and t-tests were performed for continuous data, controls and OA groups, and between OA groups, respectively. χ^2 tests were performed for categorical data.
* $P < 0.05$.
† $P < 0.001$.
6MWT, 6-Minute Walking Test; ADL, activities of daily living; ANOVA, analysis of variance; BMI, body mass index; DN4, Douleur Neuropathique en 4 questions; HADS, Hospital Anxiety and Depression Scale; HOOS, Hip Injury and Osteoarthritis Outcome Score; KOOS, Knee Injury and Osteoarthritis Outcome Score; KL, Kellgren–Lawrence scale; NRS, numeric pain rating; PCS, Pain Catastrophizing Scale; SR, sports and recreation; TUG, stand up and go test; QoL, quality of life.

cortex/paracingulate gyri were identified, differentiating the 3 groups (**Table 2**). Post hoc analyses (Tukey HSD test) revealed statistically significantly reduced regional volume only for HOA when compared with KOA and controls ($P < 0.001$). Knee osteoarthritis and controls did not show a statistically significant difference within this cluster ($P = 0.34$).

3.4. Hip osteoarthritis and knee osteoarthritis patients exhibit lower GM volume in primary motor cortex contralateral to osteoarthritis pain

Next, we sought to isolate the effects of OA pain on regional GM volumes. To this end, we first realigned the OA brains relative to the body part with OA pain. That is, brains were flipped across the midsagittal plane for left-side OA patient (x-axis flipping), such that the left hemisphere would correspond to the body side contralateral to OA pain for all patients. We then performed whole-brain, voxel-wise analyses using one-way ANCOVAs across the 3 groups for VBM outcomes. Using the same criteria for statistical significance as above (ie, $\alpha = 0.001$), we identified 5 statistically significant clusters (**Fig. 2A** and **Table 2**). Post hoc analysis of these clusters revealed: (1) relative to healthy controls, both OA groups exhibited lower volumes in left primary motor cortex (precentral cortex), as well as in the left temporal pole; and (2) relative to healthy controls, KOA, but not HOA, had lower GM volume in the precuneus cortex and increased GM volume in the

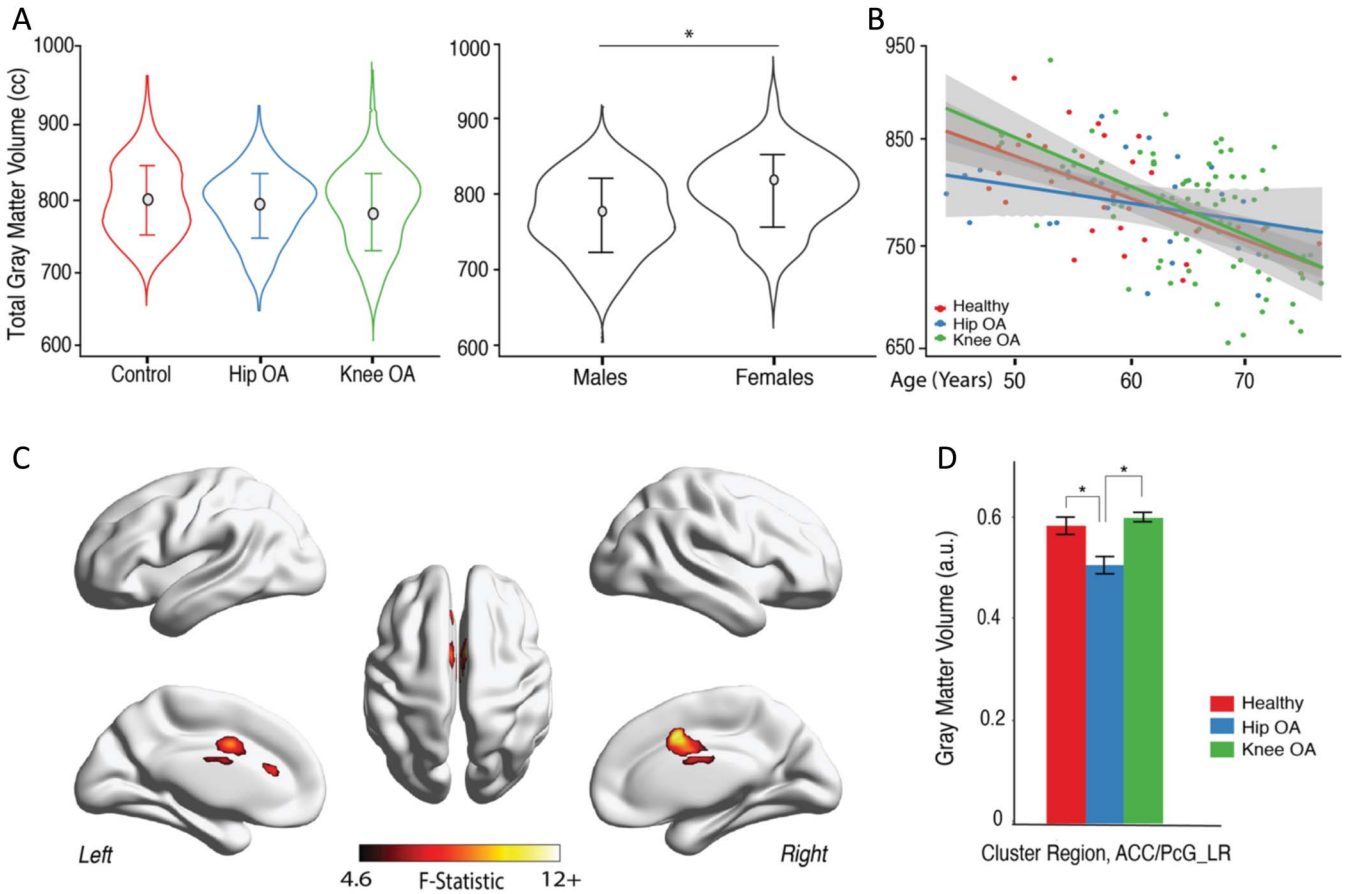

Figure 1. Whole-brain cortical gray matter changes reflect lower volumes in anterior cingulate, paracingulate gyri in HOA. (A) Average total neocortical gray matter (TGM) matter volume was not different between healthy controls, HOA, and KOA patients (age, sex, and intracranial volume were used as confound variables ($F(2,145) = 0.07$, $P = 0.79$)). TGM differed by sex across groups, when controlling for total IC volume and age ($F(1,145) = 15.7$, $P < 0.001$), with females showing higher volumes. (B) Scatterplot represents total neocortical GM in relation to age for each subject, color-coded by group; slopes were computed for each group, showing decrease of TGM with age, for all groups ($P < 0.05$; R2: controls = 0.52; KOA = 0.37; HOA = 0.17). (C) Gray matter morphological changes assessed by voxel-based morphometry (VBM). The 3 groups were contrasted together, using a 1-way between-subjects ANCOVA, with age, sex, and total ICV as covariates of no interest. Shown is the F-test statistical map, clustering determined using uncorrected *P*-value binarized at value of 0.001 and cluster size >66 voxels. Only cingulate/paracingulate gyri showed regional GM volume difference between the groups. (D) Post hoc results for GM volume comparisons in the identified region—anterior cingulate/paracingulate gyri (ACC/PcG_LR). Bars represent the mean gray matter volume and error bars represent the standard error. Tukey HSD test showed regional GM volume was lower in HOA from KOA and healthy subjects at $P < 0.001$. Knee osteoarthritis and controls did not show a statistically significant difference ($P = 0.34$). *$P < 0.001$. ANCOVA, analysis of covariance; HOA, hip osteoarthritis; KOA, knee osteoarthritis.

medial frontal gyrus. In addition, we identified lower GM volume in the anterior cingulate cortex (ACC_LR) for the HOA group relative to KOA and controls. This cluster considerably overlapped (Sørensen–Dice coefficient = 0.71) with the ACC cluster we obtained in the nonflipped analysis. The unthresholded statistical maps for native space and flipped analysis can be accessed in Neurovault.org (https://identifiers.org/neurovault.collection:6002).

Overall, by aligning the brain in relation to body side with OA pain, we observe more statistically significant clusters and stronger effects of GM volume differences between the groups. Importantly, we are able to identify the primary motor cortex region contralateral to the OA pain with lower GM volume in both knee and HOA patients.

3.5. Lack of relationship between clinical variables for clusters identified by voxel-based morphometry

To elucidate the clinical relevance of the GM volume differences among HOA, KOA, and healthy controls (6 clusters, before and after brain flipping), we correlated clinical characteristics of OA with GM volumes. The relationship between cluster GM volumes and clinical variables was calculated using partial correlations, controlling for age, sex, and TICV. We did not find any statistically significant relationships ($|r| \leq 0.28$; (Table S2, available online as supplemental digital content at http://links.lww.com/PAIN/B8).

3.6. Univariable and multivariable GM volume relationships associated with osteoarthritis, after parceling the brain into Brodmann areas

The above analyses were done at the voxel level. To reduce dimensionality, we studied GM properties across the groups and as a function of clinical characteristics after parceling the brain into ROIs approximating Brodmann areas (AAL atlas). GM volume differences were studied at this larger scale by subdividing the brain into 90 predefined regions (approximating 45 left and 45 right brain Brodmann areas) and calculating the mean GM volume for each ROI. Reduced dimensionality enabled studying OA-related brain volume differences with a multivariable approach, which considers the inter-relationships between regional GM volumes.

Table 2

Clusters for GM volume differences in HOA, KOA, and healthy controls for whole brain analysis with and without brain flipping based on OA body side dominance (x-axis).

Peak MNI coordinate region (Harvard-Oxford Cortical Structural atlas)	Peak (max) F value	No. of voxels	Peak MNI coordinate
Nonflipped brain (Fig. 1C)			
Paracingulate gyrus (20%); cingulate gyrus, anterior division (14%); juxtapositional lobule cortex (7%)	12.4	888	(12,8,8)
Cingulate gyrus, anterior division (93%)	8.58	51	(−2,32,16)
Flipped brain (Fig. 2A)			
Cingulate gyrus, anterior division (9%), posterior division (4%)	18.8	1224	(8,−8,32)
Precentral gyrus (54%)	7.55	136	(−28,−18,70)
Temporal pole (34%)	9.06	122	(34,8,−34)
Precuneous cortex (49%), intracalcarine cortex (72%)	13.2	84	(12,−58,10)
Middle frontal gyrus (42%), superior frontal gyrus (2%)	10.3	76	(30,24,50)
Middle frontal gyrus (23%), superior frontal gyrus (2%)	8.45	30	(−38,2,64)
Frontal orbital cortex (88%)	10.5	27	(−22,26,−20)
Heschl gyrus (22%)	10.9	24	(−42,−28,8)
Precentral gyrus (64%), middle frontal gyrus (2%)	6.72	14	(−52,−4,50)

All identified clusters from VBM GLM analysis, TFCE uncorrected $P < 0.001$. Cluster peak coordinates (x,y,z) are displayed according to MNI atlas, labels accordingly to the Oxford-Harvard Structural Cortical Atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). We accepted clusters greater than 66 voxels in size for post hoc analysis, given the Gaussian Kernel (FWHM = 8 mm) used for smoothing.
HOA, hip osteoarthritis; KOA, knee osteoarthritis; OA, osteoarthritis; VBM, voxel-based morphometry.

First, differences in GM volume across the 3 groups were examined for each ROI in the native and appropriately flipped brains (rendering OA pain to be left body side lateralized) using a one-way ANCOVA (**Figs. 3A and B**). Multiple regions that attained statistical significance were identified ($P < 0.001$): left putamen in the native brain analysis; bilateral pallidum, precentral left cortex, and 2 right frontal regions (rectus and lingual gyrus) for the flipped brain analysis. After FDR correction for multiple comparisons, only left precentral cortex yielded statistical significance ($F = 5.9$, corrected $P < 0.05$). Post hoc analysis for this ROI showed decreased volume for both OA groups when compared with controls (Tukey HSD tests, $P < 0.01$), but not between OA groups ($P = 0.73$), showing a pattern concordant with the results obtained in the voxel-wise analysis.

We next sought to study GM volumetric differences in a multivariable space using logistic regression to classify OA patients and controls based on 90 ROIs. To enforce sparsity and reduce overfitting, we used L1 regularization (LASSO) to drive coefficients towards zero. We took advantage of the large number of KOA patients and subdivided this group into training and test groups to ensure generalizability and unbiasedness. Results obtained in the training group were tested on the hold-out

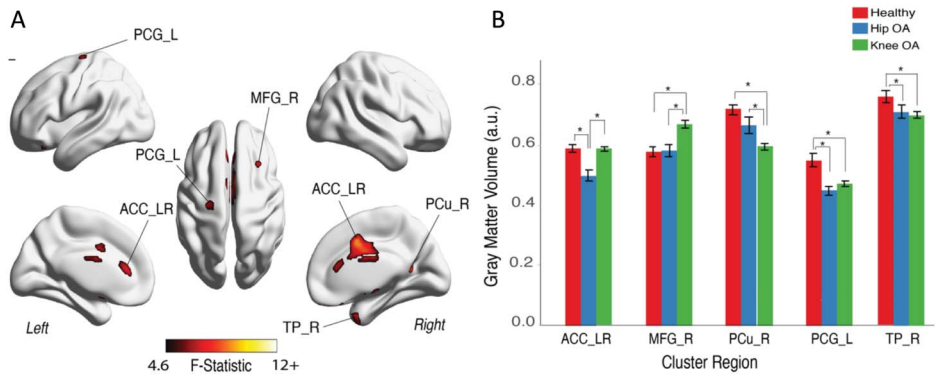

Figure 2. Primary motor cortex, contralateral to OA pain, showed lower volume in both HOA and KOA patients. (A) Gray matter morphological changes assessed by voxel-based morphometry (VBM) after aligning the brain in relation to OA pain (brain x-axis left-to-right flipping for left sided KOA and HOA, which renders the left hemisphere to be contralateral to OA in all patients). The 3 groups were contrasted together, using a 1-way between-subjects ANCOVA, controlling for age, sex, total ICV, and brain flipping. Shown is the F-test statistic map clustering determined using a TFCE uncorrected *P*-value binarized mask at value of 0.001 and cluster size >66 voxels. Multiple brain regions showed changes in regional volume (B). Post hoc results for GM volume differences for significant clusters, adjusted for age, sex, and TICV (Tukey HSD tests at $P < 0.001$); bars represent the mean gray matter volume and error bars represent the standard error. Left primary motor cortex (precentral gyrus; PCG_L) and right temporal pole (TP_R) presented lower GM volume in both OA groups. Bilateral anterior cingulate cortex (ACC_LR) showed lower GM volume only in HOA, when contrasted with the other 2 groups. In the KOA group, GM volume was greater for middle frontal gyrus cluster on the right (MFG_R) and lower for right precuneus cortex (PC_R). Further information on thresholded clusters can be found in Table 2. *$P < 0.001$. HOA, hip osteoarthritis; KOA, knee osteoarthritis; OA, osteoarthritis; TICV, total intracranial volume.

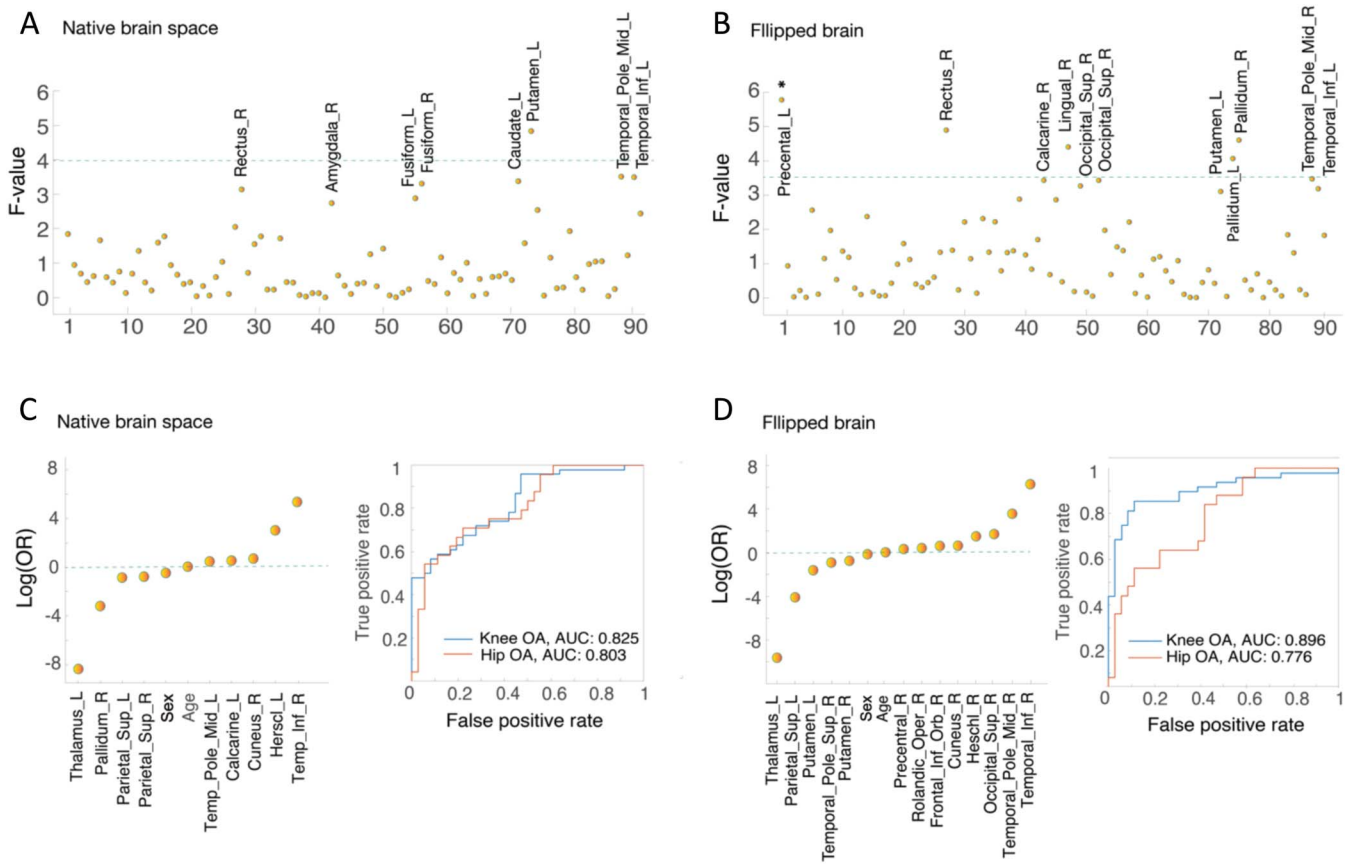

Figure 3. Univariable and multivariable analysis of regional GM differences between groups. Cortex was subdivided into 90 ROIs approximating Brodmann areas, using the AAL atlas; A and B plots show the F-value for each ROI across group comparison in native space, without brain flipping (A) and after flipping the brains (B) based on OA body side dominance (x-axis). Age, sex, TICV, and OA side in lateralized analysis were entered as covariates of no interest. Green line indicates uncorrected significance threshold at $P < 0.01$ ($F(3,148) > 4$ and $F(4,127) > 3.5$ for A and B); brain regions above and close to uncorrected threshold are labeled and include subcortical regions, temporal, and frontal regions. Primary motor cortex was identified solely in the flipped brain analysis (B) and was the only region surviving FDR correction for multiple comparisons (*$P < 0.05$). (C and D) The coefficient estimates (log(odds)) in KOA training group after LASSO regularization with lambda selection through 10-fold cross-validation for native (C) and in flipped volumes (D). Receiver operating characteristic for classification by logistic regression for the test KOA group and HOA group are also reported (blue = KOA; red = HOA). Areas under the curve showed values between 0.77 and 0.90, suggesting that generated models were not overfit and selected parameters are relevant predictors of OA-related brain morphological properties. HOA, hip OA; KOA, knee OA; OA, osteoarthritis; LASSO, least absolute shrinkage and selection operator; ROI, region of interest; TICV, total intracranial volume.

test group. **Figures 3C and D** show multivariable model results for the training KOA sample in native space (**Fig. 3C** left panel) and for flipped brain analyses (**Fig. 3D** left panel). Age and sex, although having small influences (0.24-0.06 log(OR)) were captured in both models. In addition, the combination of lower GM volumes of the left thalamus and parietal superior left cortex and higher GM volumes of temporal inferior gyrus together were strong predictors for KOA classification in both models. The flipped brain model captured additional regions not observed in the native analysis, including lower GM volumes in bilateral putamen, and higher GM volumes in right precentral gyrus and in frontal inferior orbicular gyrus.

We tested the performance of the classification models in the KOA hold-out sample to test validity of obtained results, and in HOA sample to test for generalization from KOA to HOA. For the hold-out KOA group, an AUC of 0.82 (nonflipped analysis) and 0.89 (flipped brain analysis) was attained. When evaluated in the HOA group, logistic regression presented an AUC of 0.8 and 0.77 for nonflipped and flipped analyses, respectively. Receiver operating characteristic curves are displayed in **Figure 3C** (right panel) and **Figure 3D** (right panel). Probability plots for each model are presented in Figure S1 (available online as supplemental digital content at http://links.lww.com/PAIN/B8).

Finally, we tested the model's performance for classifying among OA groups. The obtained AUC's were 0.65 and 0.76 for the nonflipped and flipped models, respectively (probability plots, Figure S2, available online as supplemental digital content at http://links.lww.com/PAIN/B8). Multivariable models seem both valid and generalizable from KOA to HOA, with the flipped model showing higher specificity for KOA.

3.7. Neuropathic pain associated with multivariable model for knee osteoarthritis

Given that the flipped brain multivariable model could better distinguish between OA and healthy controls, also showing higher specificity for knee OA, we further examined this model (**Fig. 4A**). First, we used Neurosynth database meta-analytical decoding to identify psychological/task terms associated with brain activity in these regions. We decoded the regions as absolute values, reflecting only location (**Fig. 4B**), and also using weighted values to account relative contribution of different regions in the model (**Fig. 4C**). The top 5 terms associated with the model for location only were: dementia, personality, gestures, social interaction, and interpersonal relations. When incorporating the model coefficient of each area, the main terms identified were pain, anticipatory, finger tapping, index finger, and integrate.

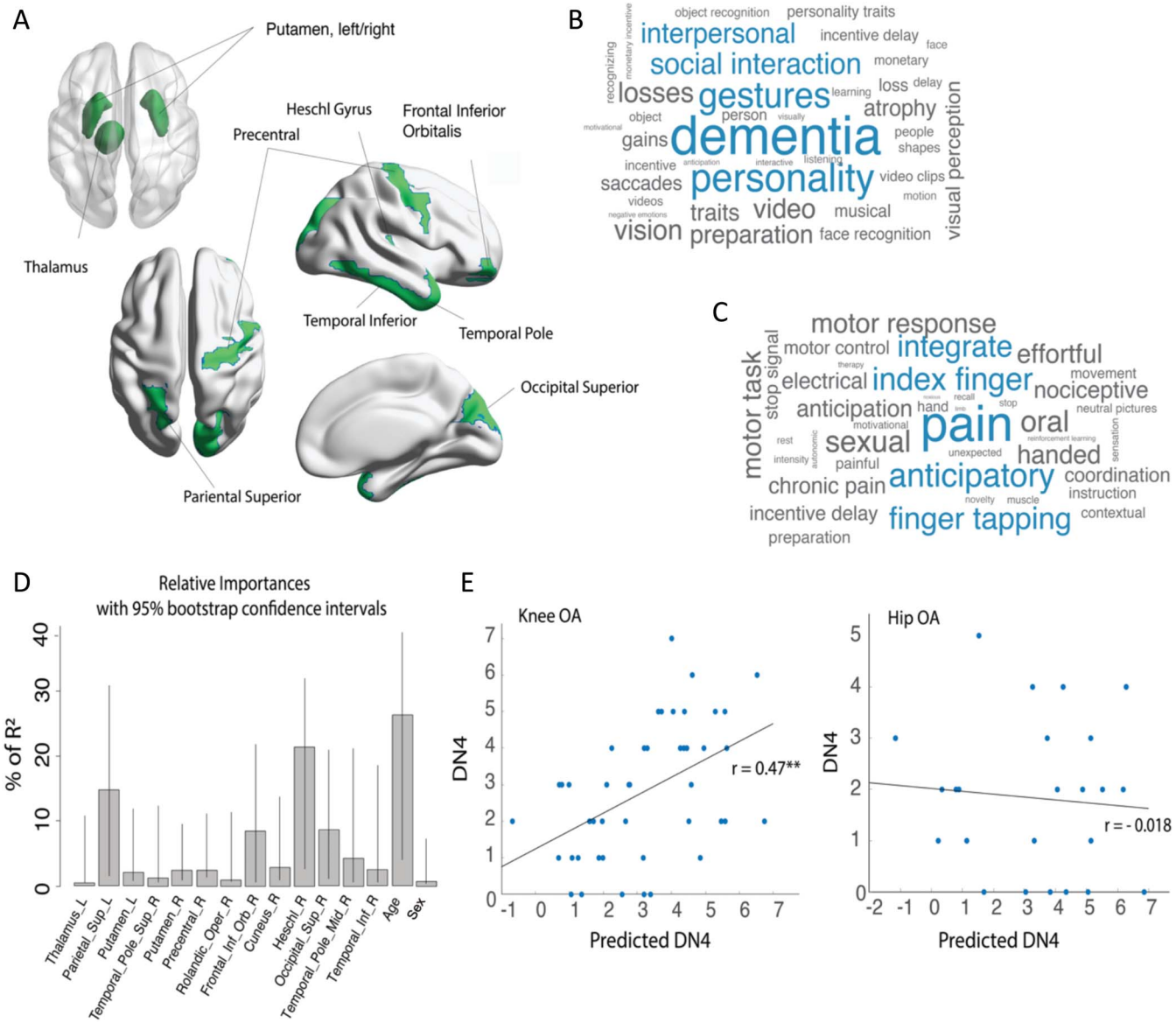

Figure 4. Neuropathic pain profile was associated with KOA multivariable brain volume changes. (A) Graphic representation of the AAL ROIs identified in the multivariable analysis (flipped brain). (B and C) plots show the top 40 (of about 1700) correlated psychological/task terms using Neurosynth reverse inference decoder for the brain regions (B) and weighted regions, given the model estimate coefficients (C). The size of a term in each word cloud is proportional to the correlation strength of term/region. Blue color represents top 5 correlations. (D–E) A multiple regression model using the logistic regression/LASSO results for flipped brain KOA classification predicted neuropathic pain score (DN4) in a subsample of KOA patients (training sample, n = 45). This result was validated on a KOA hold-out sample (test sample, n = 46), but not in the HOA group. (C) The relative importance of all predictive variables where % of R^2 is normalized to sum 100%. Bars correspond to 1000 bootstrap confidence intervals at 95%. (E) The validation of the obtained regression model in KOA testing sample and HOA groups. Predicted neuropathic pain scale (DN4) strongly and significantly correlated with the actual score in the KOA test group, but not in the HOA. DN4 (Douleur Neuropathique en 4 questions); $^{**}P < 0.001$. HOA, hip osteoarthritis; KOA, knee osteoarthritis; LASSO, least absolute shrinkage and selection operator; ROI, region of interest.

In an unbiased approach, we tested the model's association with clinical aspects of pain and mobility in OA. Using the KOA training sample (n = 45), and the predictors obtained from the LASSO, multiple regression models were built for each clinical variable of interest (ie, pain duration; pain intensity; HADS anxiety; HADS depression; Pain Catastrophizing Scale; 6MWT; timed up and go; DN4 and KOOS subscales). Only one model yielded statistical significance: neuropathic pain scale, DN4 ($F(1,45) = 2.29$; Adj R2 = 0.29; $P = 0.03$). Details for all generated models can be found in Table S3 (available online as supplemental digital content at http://links.lww.com/PAIN/B8). Finally, because several models were generated and thus spuriousness of the DN4 model is highly feasible, we sought to better characterize and unbiasedly validate the DN4 model. To do so, we first calculated the relative importance for each predictor variable and computed its respective 95% confidence interval using 1000 bootstrap replicates (**Fig. 4D**). Age, parietal superior cortex, Heschl/S2 gyrus, and frontal inferior orbitalis cortex presented the highest percentage of explained variance, with smaller contributions from other brain regions. We then validated the model in the KOA hold-out sample (n = 45), where the correlation between DN4 and predicted DN4 was statistically significant and strong ($r = 0.47$, $P < 0.001$). The model failed to replicate in the HOA group ($r = -0.018$, $P = 0.93$; **Fig. 4E**). Therefore, the obtained multivariable model reflects neuropathic pain characteristics, and the model is valid for neuropathic pain in KOA but does not generalize to HOA.

4. Discussion

Our univariate analyses highlight primarily lower GM volume in HOA in the anterior cingulate, and lower GM volume in the precentral cortex in both KOA and HOA contralateral to OA pain. In addition, the multivariable analysis reveals GM distortions captured as a multidomain system that integrates cortical and subcortical structures, shared between KOA and HOA. Reverse inference of this multidomain distortion, from functional brain space to psychological and task-related terms, identified 2 sets of concepts: (1) for unweighted location analysis associated terms included dementia, personality, gestures, social interaction, and interpersonal relations; (2) when the same analysis was performed taking into consideration the weights of contributing regions, the top associated concepts were: pain, anticipatory, finger tapping, index finger, and integrate. We found that the multivariable set of regions was associated with patient-reported neuropathic pain in KOA, but not in HOA patients. Importantly, the latter group has shorter pain duration and lower neuropathic pain scores. Our univariable analysis demonstrates more widespread and stronger GM distortions when taking into account the laterality of OA; however, no statistically significant relationships were found between univariable (VBM) results and clinical variables, similar to previous reports in the field.[2,39]

Brain structural changes using GM indices in chronic pain have been reported by multiple groups, primarily using VBM. Disparate regions, both directions of GM change, and even null findings are reported.[13] Our study was designed with the purpose of characterizing brain structural properties in the largest OA population reported to date. Our results are, in part, consistent with earlier reports: decreased GM in ACC seen in HOA has also been described in the past[51]; decreased precentral GM seen here in KOA and HOA is consistent with a report of functional remodeling of the motor cortex in KOA patients.[53] Importantly, we did not observe significant GM changes (univariable analysis) in brain areas previously reported for OA VBM studies, including both subcortical (thalamus,[25] amygdala and nuclei accumbens,[34] and caudate nuclei[39]) and cortical areas (insular cortex and dorsolateral prefrontal cortex[51]). Incongruent findings across studies may relate to the heterogeneity of OA pain at distinct stages of the disease, but also to the potential inherent limitations of VBM; eg, the sensitivity of VBM to imaging parameters and scanner differences, in addition to analytical details, such as spatially normalizing atypical brains and limitations of univariate techniques.[7,40]

Our multivariable analysis indicates the existence of a common set of brain distortions between KOA and HOA that differentiate these patients from healthy controls: 9 to 13 brain areas, composed of both cortical and subcortical regions. There is accumulating evidence that chronic pain leads to whole-brain global reorganization.[13] Tested specifically in OA patients, pain was associated with whole-brain degree rank order disruption,[38] and changes in large-scale brain network temporal dynamics.[16] Bridging this concept to morphologic brain reorganization in OA, we examined the GM volumetric distortions in a multidimensional space, accounting for the interrelationship between regions. Classification models were generated in a KOA sample, both in native and flipped brain space, and tested in hold-out KOA and HOA groups. Interestingly, the native space model yielded similar accuracy for knee and hip patients. Accuracy improved for the KOA group in the flipped brain space.

To better characterize this model, we identified the terms in the brain imaging literature associated with these regions using Neurosynth Image Decoder and selected the top 40 (of about 1300 terms) nonanatomical terms. The method uses meta-analysis (exploring around 14,000 brain imaging studies) to identify psychological and task-related terms associated with the collection of brain regions included in the multivariable model. The reverse association for the unweighted multivariable model identifies cognitive, interpersonal, and social interaction concepts, not obviously related to OA. Remarkably, when the weighted multivariable model was examined, the top term was pain (chance probability of this observation is near 1 in 1300 = 0.0008); additional pain-related terms, including chronic pain as well as motor-related terms, were also captured. This result is noteworthy because Neurosynth explores brain activity in a heterogeneous population and yet identifies pain and motor properties in the weighted multivariable model.

When studying the relationship between clinical measures and LASSO-derived multivariable models, we show that neuropathic pain probability, measured with the DN4 scale, is associated with the set of identified variables in the KOA group. Using an unbiased approach, we demonstrated that this result validates in the KOA sample but fails to generalize for HOA patients. This finding deserves a thorough examination: (1) KOA patients show a higher probability of neuropathic pain than HOA, fact that has been previously described[11]; (2) interestingly, in our sample, KOA patients also showed a longer pain duration, but less severe radiographic damage.

These results are concordant with Dabare et al.,[17] who showed that HOA symptomatology clinically presents later with more advanced disease than KOA, and patients are likely to undergo arthroplasty earlier from the time of presentation. Our findings suggest that, together with longer pain duration, there is the emergence of a neuropathic pain profile that can be clinically identified and linked to brain GM morphological properties. Our present result cannot unequivocally establish whether the multivariable GM distortion is a prognostic or diagnostic of neuropathic pain. However, the temporal dissociation between knee and hip pain and radiographic damage, together with a shared GM multivariable model, suggests that the model is more likely to be prognostic risk factor for developing signs of neuropathic pain in OA.

In a recent report based on the same KOA and HOA patient cohort, we examined the relationship between OA pain and clinical parameters.[10] Although multiple models could be derived for different measures of OA pain, these were not consistent and thus were deemed unstable and uninformative. Here, we queried the univariate and multivariable GM distortions associated with OA regarding their relationship to clinical characteristics. Univariate brain distortions were more prominent in the hemisphere contralateral to OA pain, and the neuropathic pain scale was related to the multivariable model, yet the majority of clinical parameters associated with OA were unrelated to GM distortions. This raises the question whether observed GM distortions can be seen as prognostic or diagnostic. Within the conceptual construct of the four-stage model for transition to chronic pain,[49] formulated based on a longitudinal study of back pain patients,[8] we have proposed a set of criteria that would differentiate between prognostic and diagnostic biomarkers for chronic pain: prognostic biomarkers should be preexisting factors that influence transition to chronic pain but are not modulated by pain. Conversely, diagnostic biomarkers are emergent in time with the transition to chronic pain and should reflect pain and related clinical characteristics. If we presume that the transition to chronic pain for OA, relating to its persistence after joint replacement surgery, follows the same general model as in back pain, then a lack of relationship

between clinical parameters and GM abnormalities suggests these are more likely to be prognostic in nature. This notion should be especially true for brain regions or multivariable models that show distortions shared between KOA and HOA as the impact of OA pain in HOA is distinct from that for KOA,[10] which in turn should differentially distort GM in areas reflecting diagnostic consequences.

This study does not come without limitations. Results from the VBM analysis should be cautiously interpreted because identified clusters result from uncorrected whole-brain analysis; however, our report is in line with previous publications on brain morphometry in chronic pain, reporting group comparisons at uncorrected $P < 0.001$.[2] We limit reporting only large cluster GM abnormalities (>66 voxels) to minimize false-positive findings. Another important limitation that has to be highlighted is the imbalance in the number of subjects between OA groups and controls. Although such an imbalance limits our statistical power,[15] our knee group was sufficient to construct the multivariable models using half of the knee patients. However, this is in contrast to the control group, which was not large enough to split, and thus, it was used in both the training and test set. Another shortcoming of this study is the fact that controls are not perfectly matched regarding age and sex with our KOA group; however, we account for the effect of these variables in all stages of our analysis. Finally, socioeconomic and cultural differences regarding attitudes of coping and/or suffering with OA pain may also underlie differences in VBM results when contrasting our findings with other studies.

In conclusion, our results show decreased GM in HOA in the ACC and decreased GM in precentral cortex in both KOA and HOA; however, these GM differences are not strongly correlated with clinical variables in OA. Moreover, we derived a multivariable model based on GM distortion that differentiated OA patients from healthy subjects. Importantly, this model was associated with the neuropathic scale in KOA, and in reverse inference, it was linked with pain and motor control in the brain imaging literature. We reason that observed GM distortions may reflect a priori risks for chronicity of OA pain rather than being consequential to the development of the disease.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B8.

Supplemental video content

A video abstract associated with this article can be found at http://links.lww.com/PAIN/B9.

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