Research Paper

PAIN®

Subcortical brain anatomy as a potential biomarker of persistent pain after total knee replacement in osteoarthritis

Joana Barroso[a,b,c,d,e], Paulo Branco[d,e], João Pinto-Ramos[f], Andrew D. Vigotsky[d,e,g], Ana Mafalda Reis[h], Thomas J. Schnitzer[c,e,i,j], Vasco Galhardo[a,b], A. Vania Apkarian[c,d,e,j,*]

Abstract

The neural mechanisms for the persistence of pain after a technically successful arthroplasty in osteoarthritis (OA) remain minimally studied, and direct evidence of the brain as a predisposing factor for pain chronicity in this setting has not been investigated. We undertook this study as a first effort to identify presurgical brain and clinical markers of postarthroplasty pain in knee OA. Patients with knee OA (n = 81) awaiting total arthroplasty underwent clinical and psychological assessment and brain magnetic resonance imagining. Postoperative pain scores were measured at 6 months after surgery. Brain subcortical anatomic properties (volume and shape) and clinical indices were studied as determinants of postoperative pain. We show that presurgical subcortical volumes (bilateral amygdala, thalamus, and left hippocampus), together with shape deformations of the right anterior hippocampus and right amygdala, associate with pain persistence 6 months after surgery in OA. Longer pain duration, higher levels of presurgical anxiety, and the neuropathic character of pain were also prognostic of postsurgical pain outcome. Brain and clinical indices accounted for unique influences on postoperative pain. Our study demonstrates the presence of presurgical subcortical brain factors that relate to postsurgical persistence of OA pain. These preliminary results challenge the current dominant view that mechanisms of OA pain predominantly underlie local joint mechanisms, implying novel clinical management and treatment strategies.

Keywords: Osteoarthritis, Chronic pain, Postsurgical pain, Subcortical brain

1. Introduction

Osteoarthritis (OA) is one of the most prevalent musculoskeletal diseases[42] and its prevalence is projected to increase.[33] Total knee replacement (TKR) is commonly performed to treat the disease when pharmacological and conservative treatments cannot provide adequate pain relief and level of function.[29] In 2018 alone, around 715,000 TKR[22] surgeries were performed in the United States and the annual use of TKR procedures is expected to increase by 400% by 2040.[52] Although TKR is seen as a highly successful surgery,[59] an important proportion of patients still report pain post-TKR.[14,26]

Clinical, demographic, and psychologic factors have been proposed as risk factors for persistent pain in patients undergoing TKR[31]; eg, anxiety and depressive symptoms, pain catastrophizing,[4,26] coping strategies,[13] higher levels of presurgical pain,[51] and neuropathic quality of pain.[23] Presurgical pain thresholds obtained from quantitative sensory testing (QST) have also been proposed as predictors of pain persistence after TKR in OA.[60] Although psychosocial factors and QST do not evaluate the same construct,[4] these variables are usually considered proxies of altered central pain modulation in OA, and while central sensitization has been associated with pain persistence after TKR, it has mostly been studied at the spinal cord and antinociceptive descending modulation levels.[34]

Brain structural and functional changes associated with OA have been described: differences in brain cortical and subcortical anatomic indices between healthy controls and patients with OA,[9,36] whole-brain reorganization of resting-state functional connectivity,[35] and major changes in information sharing within sensory motor regions and the insular cortex.[11] Nevertheless, direct evidence of brain properties as a precursor to OA pain persistence after TKR is still lacking. By contrast, the importance of brain mechanisms for the persistence of low back pain has been better characterized, with corticolimbic white matter connectivity, anatomical properties of the amygdala and hippocampus,[58] and functional connectivity between corticolimbic regions being implicated in the progression from acute to chronic pain.[6,58] Our current knowledge of brain adaptations in OA pain and brain corticolimbic characteristics as prognostic factors for persistent pain[8] suggests that pain in OA may be contingent on

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Departamento de Biomedicina, Faculdade de Medicina, Universidade do Porto, Porto, Portugal, [b] Instituto de Investigação e Inovação em Saúde—i3S, Universidade do Porto, Porto, Portugal, Departments of [c] Physical Medicine and Rehabilitation and, [d] Neuroscience, Northwestern University, Feinberg School of Medicine, Chicago, IL, United States, [e] Center for Translational Pain Research, Center of Excellence for Chronic Pain and Drug Abuse Research, Northwestern University, Feinberg School of Medicine, Chicago, IL, United States, [f] Centro Hospitalar e Universitário de São João, Porto, Portugal, [g] Departments of Biomedical Engineering and Statistics, Northwestern University, Evanston, IL, United States, [h] Unilabs Boavista, Porto, Portugal, Departments of [i] Rheumatology and, [j] Anesthesiology, Northwestern University, Feinberg School of Medicine, Chicago, IL, United States

**Corresponding author. Address: Northwestern University, Feinberg School of Medicine, Tarry Bldg. 7-705, Chicago, IL 60611, United States. Tel.: (312) 503-0404; fax: (312)503-5101. E-mail address: a-apkarian@northwestern.edu (A. V. Apkarian).*

PAIN 00 (2023) 1–10

© 2023 International Association for the Study of Pain

http://dx.doi.org/10.1097/j.pain.0000000000002932

Copyright © 2023 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

both peripheral nociceptive signaling *and* brain properties. Chronic OA is also characterized by significant impact in physical function, motor control, action planning, and proprioceptive changes.[28,55] We[9] and others[21,36] have shown anatomical dissimilarities in the thalamus, putamen, and caudate in patients with knee OA vs controls.

We followed patients with knee OA scheduled for TKR (n = 81), from before to 6 months after surgery; performed preoperative brain anatomical scans using magnetic resonance imaging (MRI); and collected OA clinically related indices and questionnaires. In this first effort to study brain biomarkers of postsurgical OA pain, we focus on brain subcortical structural properties, namely, volume and shape. Our main hypothesis, in line with research in chronic back pain (CBP) patients, is that preoperative anatomic characteristics of subcortical regions including the amygdala, hippocampus, and nucleus accumbens are associated with pain persistence in patients with OA after surgery. Moreover, given the clear impact of OA on physical function and motor or action planning, we further examine the contribution of the dorsal striatum, pallidum, and thalamus in postsurgical pain.

2. Methods

2.1. Study design

The present work is part of a longitudinal observational project in which a convenience sample of patients with osteoarthritis was evaluated before joint replacement surgery and followed for 6 months after surgery.[10] The protocol constituted a total of 4 visits: 1 to 3 months before surgery (visit 1), a second presurgical visit 2 to 6 weeks before surgery (visit 2), and 2 postsurgical visits at 3 and 6 months after surgery (visits 3 and 4, respectively). Visits 1, 3, and 4 consisted of a clinical evaluation and multiple pain, mood, and general health questionnaires; brain MRI scans were performed at visits 2 and 4. Only patients who completed the 4 visits were included in this report (n = 82), and only MRIs collected at visit 2 were analyzed.

2.2. Participants (study population)

Participants included in this study were patients with knee OA with a clinical indication for TKR surgery, recruited at the orthopedic surgery department, *Centro Hospitalar e Universitário de São João*, Porto, Portugal. The study protocol was approved by the local ethics committee, and all participants provided written informed consent before initiating the study.

Inclusion criteria were age between 45 and 75 years, knee OA diagnosis according to the clinical classification criteria of the American College of Rheumatology,[46] and clinical indication for TKR surgery by a certified orthopedic surgeon in our center. Exclusion criteria were evidence of secondary osteoarthritis due to congenital or development disease, inflammatory, or autoimmune disorders; indication for bilateral arthroplasty or bilateral knee pain with ≤4 points difference (numeric rating scale [NRS]) between the 2 joints; other chronic pain conditions (eg, fibromyalgia, chronic pelvic pain, and chronic headache); chronic neurological or psychiatric disease (eg, dementia, Parkinson disease, demyelinating diseases, major depressive disorder, obsessive compulsive disorders); and previous history of stroke or traumatic brain injury.

2.3. Clinical outcomes

The main clinical outcome of the study was the NRS for pain over the previous week. All patients completed a battery of questionnaires assessing multiple domains: Knee Injury and Osteoarthritis Score (KOOS),[19] Hospital Anxiety and Depression Scale (HADS),[40] Pain Catastrophizing Scale (PCS),[56] and Neuropathic pain scale (DN4).[15] Physical performance was assessed with 2 tasks: timed up and go test (TUG)[44] and six-minute walking test (6MWT).[47] Knee x-rays were reviewed by 2 radiologists and classified using the Kellgren–Lawrence scale.[25] Because KOOS-P and SF-36 are on a 0 to 100 scale, with higher values indicating *less* pain, we transformed and inverted them to a 0 to 10 scale ($x^* = \frac{100 - x}{10}$) in which higher values indicated *more* pain, following the same direction as the NRS.

2.4. Magnetic resonance imaging acquisition and data quality control

MPRAGE T_1-anatomical brain images were acquired with a 3.0-T Siemens Magnetom Spectra scanner (Siemens Medical, Erlangen, Germany). Acquisition parameters: time of repetition (TR) = 2500 milliseconds, echo time (TE) = 3.31 milliseconds, flip angle = 9°, field-of-view (FOV) = 256 × 256 mm^2, voxel size = 1 × 1 × 1 mm, and number of slices = 160.

Individual T1-weighted structural images were visually inspected for technical artifacts. Contrast to noise ratio (CNR) for gray matter was calculated for each subject and we used mean CNR minus 2 standard deviations as a threshold for group outliers. No subjects were excluded given these criteria.

2.5. Statistical analysis

To classify pain surgery outcome—OA recovering (OAr) and OA persisting (OAp)—we evaluated pain scores before and 6 months after surgery. First, we visually inspected the distribution of absolute pain scores after surgery for 3 different scales: NRS, KOOS pain, and SF-36 pain. Next, using the same cutoff for classification for the 3 scales, we evaluated the accuracy of classification between them, along with its 95% confidence intervals calculated using 1000 bootstraps for each model (basic bootstrap or reverse percentile method). Finally, we assessed the agreement between absolute NRS score and percent change from baseline using the same methodology as described above.

For demographic and clinical data, comparisons between OA groups were made using analysis of variance (ANOVA) and independent sample *t*-tests or χ^2 tests for continuous variables and categorical data, respectively. Finally, we compared all clinical variables at baseline using analyses of covariance, adjusting for initial pain levels, with OA groups as between-subject factor. Benjamin–Hochberg correction of the false discovery rate (FDR) for multiple comparisons was applied.[12]

2.6. Magnetic resonance imagining data analysis

Subcortical volumes and shape data were analyzed with the standard automated processing stream from the FMRIB's Integrated Registration and Segmentation Tool (FIRST).[39] Visual inspection of the subcortical segmentation was performed for all subjects. No gross mismatches between underlying anatomy and FIRST outcome were identified.

The volumes of right and left amygdala, caudate, hippocampus, nucleus accumbens, putamen, pallidum, and thalamus were calculated for each subject. We choose to study the interaction between subcortical anatomical volumes and surgical pain outcomes, by using a mixed-design analysis of covariance (ANCOVA) model, where the random factor was

Copyright © 2023 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

the subjects' identity; within-subject factors were brain region volumes (7 levels: thalamus, amygdala, hippocampus, nucleus accumbens, pallidum, and caudate) and brain hemisphere (2 levels: right/left). Studying brain regions as a within-subject effect allows us to isolate the variance between participants which would result in a smaller residual error. Between-subject factors were postsurgical outcome (OAr/OAp); age, sex, initial pain level (presurgical), and total intracranial volume (estimated using FMRIB Software Library FSL SIENAX[54]) were introduced as covariates of no interest. Of principal interest was the interaction between subcortical structure (within-subject factor) and OA group (subcortical volume × OA group).

Three separate *post hoc* exploratory analyses were performed to explore the etiology of the structure by the OA group effect. The first analyses used the same model as above but explored each subcortical structure independently. The second analysis included an interaction with the hemisphere (structure by OA group by hemisphere). The third analysis included an interaction with the OA site (structure by OA group by laterality). In each, *post hoc* effects were calculated within each subcortical structure.

Next, we studied localized specific differences using vertex-wise statistics. Here, we choose to direct our analysis to the thalamus, hippocampus, and amygdala. Using FSL's FIRST, we generated a vertex representation of subcortical structures (FSL FIRST user guide [fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST])[41]: "manual labels are parameterized as surface meshes and modelled as a point distribution model. Deformable surfaces are then used to automatically parameterize volumetric labels in terms of meshes where deformable surfaces are constrained to preserve vertex correspondence for the entire training data. The shape and appearance of the model is based on multivariate Gaussian assumptions. Based on the learned models, FIRST searches through linear combinations of shape modes of variation for the

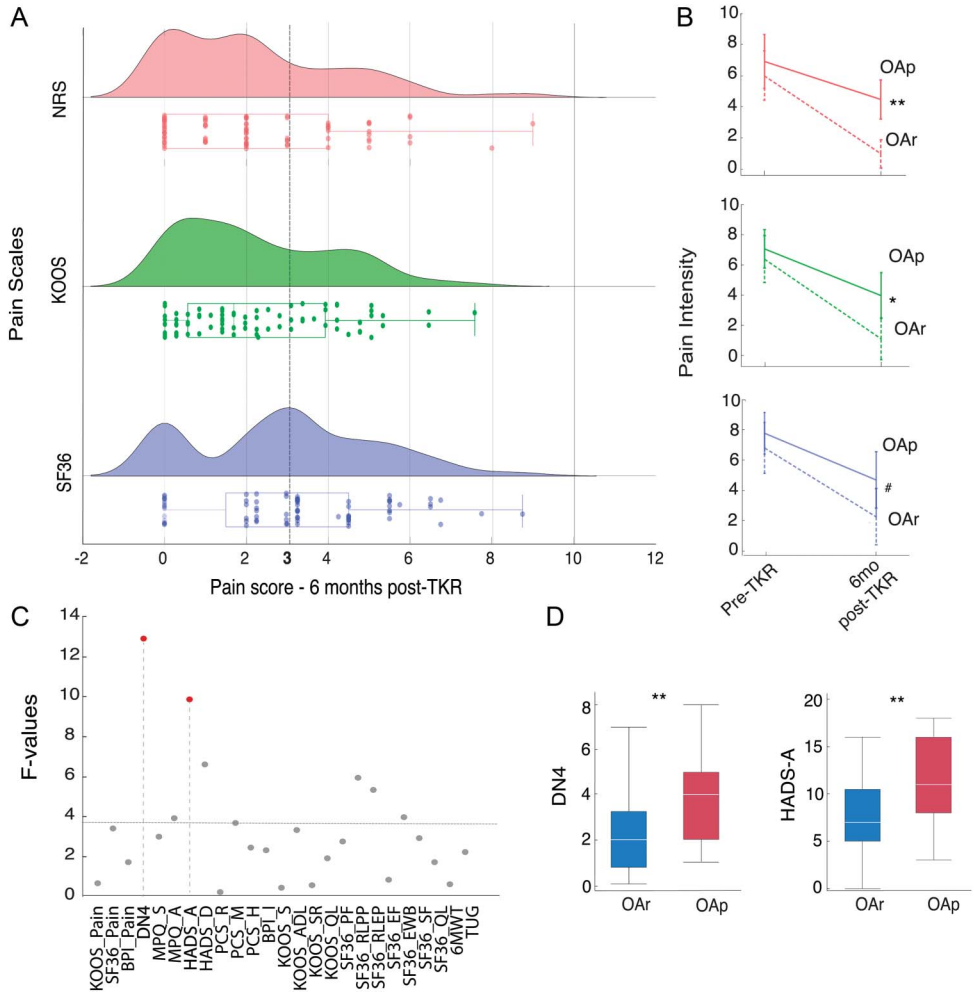

Figure 1. Classification of postoperative pain outcomes and baseline clinical data. (A) Distribution of pain scores 6 months after surgery for 3 distinct scales. The dotted line corresponds to the threshold used to classify outcomes into 2 distinct groups: OA recovering (OAr) and OA persisting (OAp). (B) Group differences at baseline and 6 months using the 3 different scales and the defined cutoff (≥3 points). At baseline, there were no differences between groups; NRS and KOOS scale showed a statistically significant difference at 6 months. (C) Presurgery clinical variables distinguishing the outcome groups. DN4 scale and HADS-Anxiety subscale (red dots) were statistically significantly different between the 2 outcome groups (OAr and OAp) after adjusting for presurgical pain levels and correcting for multiple comparisons (FDR corrected). Dotted line corresponds to uncorrected $\alpha = 0.05$. (D) Both presurgical DN4 and HADS-A presented higher values in the patients with OA progressing to persistent pain (OAp) after surgery. $^{**}P < 0.01$; $^{*}P < 0.05$; $\#P > 0.05$. 6MWT, 6-minute walking test; BMI, body mass index; DN4, Douleur Neuropathique en 4 questions; HADS, Hospital Anxiety and Depression Scale; KOOS, Knee Injury and Osteoarthritis Outcome Score (ADL, activities of daily living; SR, sports and recreation; QoL, quality of life); PCS, Pain Catastrophizing Scale (R—Rumination subscale, M—Magnification subscale, H—Helplessness subscale); KL, Kellgren–Lawrence scale; sf-36, Short-Form 36 Health Survey; PF, physical functioning; PH, physical role functioning; EP, emotional role functioning; EF, energy/fatigue; (E, emotional well-being; SF, social functioning; GH, general health; TUG, test stand-up and go.

Copyright © 2023 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

Table 1

Demographic and socioeconomic characteristics of patients categorized as recovering or persisting (osteoarthritis recovering and osteoarthritis persisting) with knee pain 6 months after total knee replacement surgery.

	OAp[26]		OAr[55]		*P*
Subjects, n (%)	27	33.3	54	66.67	
Age (y), mean, SD	65.81	5.71	65.68	6.90	0.93
Female, n (%)	23	85.48	42	77.77	0.42
BMI (kg/m^2), mean, SD	32.03	5.0	29.99	4.77	0.078
Education, n (%)					0.45
Primary education	20	73	43	80	
Secondary education	4	15.4	9	16.4	
Postsecondary education	3	11.5	2	3.4	
Smoking, n (%)	3	11.5	3	5.5	0.40
Pain duration (y), mean, SD	10.21	6.57	6.71	5.61	0.013*
Pain intensity (NRS), mean, SD	6.92	1.75	6.38	1.58	0.16
Radiographic KL, n (%)					0.50
Grade 1	1	3.8	0	0	
Grade 2	6	23.1	14	25.5	
Grade 3	13	50	25	45.5	
Grade 4	7	23.1	15	19.1	

t-tests and ANOVAs were used to test differences in continuous outcomes. χ^2 tests were applied for categorical data.
* $P < 0.05$.
ANOVA, analysis of variance; BMI, body mass index; KL, Kellgren–Lawrence scale; NRS, numeric rating scale; OAp, osteoarthritis persisting; OAr, osteoarthritis recovering.

most probable shape instance given the observed intensities in T1 images."[41] After, vertex locations for each participant were projected onto the group average surface (all 81 patients) to obtain vertex-wise displacement values for each subject—4D file that contains the associated displacement values at each of the vertices per subject (positive values indicated outward displacements from the mean surface, whereas negative values indicated inward displacements from the mean surface). Finally, using FSL's *randomise* option for nonparametric statistics, a multivariate permutation test on the displacement values of corresponding vertices provides the F values representing differences between groups (OAr/OAp). Significant clusters were determined through threshold-free cluster enhancement (TFCE)[53] using FWE Family wise error rate correction to control for multiple comparisons. Of note, and after previous analysis, total intracranial volume (TICV), age, sex, and initial (baseline pain) were used as covariates.

Finally, to evaluate whether clinical predictors and subcortical brain biomarkers were redundantly explaining the pain outcome, we constructed a series of multiple regression models (sequential regression), with each consecutive model incorporating an additional block of variables. We modeled absolute pain score after surgery (NRS, 0-10) using 4 distinct blocks. First, we adjusted for covariates of no interest (age, sex, TICV, and baseline pain); the following 3 blocks were clinical outcomes: brain volumetric properties of thalamus, amygdala, and left hippocampus; and finally, shape displacement of the right hippocampus and amygdala. R^2 changes between each step were evaluated and model comparisons were performed using ANOVAs.

2.7. Software and code

Data were preprocessed and analyzed using MATLAB 2019b (MATLAB 2019a, The MathWorks, Inc, Natick, MA) and tools from the Oxford Center for Functional Magnetic Resonance Imaging of the Brain Software Library (FMRIB, Oxford, United Kingdom; FSL version 5.0.10). Brain regions were visualized on a surface rendering of a human brain template with BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

3. Results

3.1. Pain outcomes after surgery

The selection of a cutoff for persisting vs recovering OA pain (OAp and OAr) after total knee replacement surgery can be arbitrary and remains contentious. We started by examining the coherence of different pain scales 6 months after surgery using 3 different scales: NRS, KOOS pain (KOOS-P), and SF-36 pain subscale. A clear pattern emerged with 2 subgroups at a pain intensity cutoff of 3 (on a 0-10 scale) for the 2 first scales (**Fig. 1**). We explored the robustness of this cutoff point by contrasting

Table 2

Mixed-design analysis of covariance (ANCOVA), subcortical volumes as the dependent variable; brain hemisphere and subcortical structure (7 levels) as a within-subject factor; the group as a between-subject factor; and age, sex, baseline pain level, and total intracranial volume as covariates of no interest.

Variable	Sumsq (type III)	df	F value	*P*
Within-subject				
Intercept (SCv)	7,633,583.20	5.42	3.952	0.001
SCv × OA group	**806,756.43**	**5.45**	**2.26**	**0.043***
Error (SCv)	356,386.98	75		
Between-subject				
Intercept (SCv)	6,615,513.05	1	4.881	0.030
Group (OAp/OAr)	**5,262,323.70**	**1**	**3.883**	**0.052**
Age (y)	275,340.96	1	0.203	0.653
Sex (male 0, female 1)	12,616,956.23	1	9.310	0.003
Baseline pain (NRS, 0-10)	1,339,295.47	1	0.988	0.323
TICV (mm^3)	12,139,256.76	1	8.957	0.004
Error (SCv)	101,643,170.94	75		

Of principal interest was the interaction between subcortical structure and OA group.
* $P < 0.05$.
df, degrees of freedom; FDR, false discovery rate; NRS, numeric rating scale; OA, osteoarthritis; OAp, osteoarthritis persisting; OAr, osteoarthritis recovering; SCv, subcortical volumes, mm^3; Sumsq, sum of squares (adjusted for age, sex, TICV, and baseline pain); TICV, total intracranial volume.

Copyright © 2023 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

different scales: using KOOS to classify the outcome (≥3), we achieved a mean accuracy of 0.83 (95% CI [0.76, 0.89]) in classifying NRS outcomes; for SF-36, we achieved a mean accuracy of 0.48 [0.35, 0.57]. Next, we looked at the impact of presurgical pain on the outcome by computing the percent change in pain from baseline using NRS; a mean accuracy of 0.92 [0.87, 0.97] was obtained between absolute NRS (cutoff of 3) and 50% change for classifying recovering or persisting pain.

Taken together, these findings suggest that an absolute score of NRS ≥3 after surgery is a robust threshold for categorizing OAr and OAp. This same cutoff value has been previously used in the literature to define pain outcomes after surgery, lending confidence to our classification criterion.[2,30] With this cutoff (≥3) applied to NRS 6 months after TKR surgery, 54 patients were classified as OAr and 27 as OAp.

3.2. Demographic, socioeconomic, clinical, and psychological characteristics of osteoarthritis recovering and osteoarthritis persisting patients

No significant differences for age, sex, BMI, educational level, smoking habit, or presurgical pain intensity were seen between the OAr and OAp groups (**Table 1**). However, on average, patients with OAp showed longer pain duration before surgery (mean ± SD: 10.21 ± 6.57) when compared to patients with OAr (mean ± SD: 6.71± 5.61, $P = 0.013$).

Next, we studied clinical and psychological differences between groups before surgery using multiple questionnaires. Only initial neuropathic pain, measured with the DN4 scale (F [2,81] = 12.91, $P < 0.001$), and anxiety, measured with HADS-Anxiety subscale (F [2,81], $P = 9.865$, $P = 0.002$), were distinctive among patients with OAp and OAr, after correcting for multiple comparisons (**Fig. 1**). The OAp group presented with significantly higher levels of presurgery anxiety (OAp, mean ± SD = 11.1 ± 0.794; OAr, mean ± SD = 8.033 ± 0.559) and higher scores on neuropathic pain (OAp, mean ± SD = 3.94 ± 0.374; OAr, mean ± SD = 2.289 ± 0.263). In sum, longer pain duration, neuropathic pain profile, and anxiety before surgery were associated with pain persistence after surgery.

3.3. Presurgical subcortical volumes of the bilateral thalamus, amygdala, and left hippocampus associate with pain persistence after surgery

We first examined preoperative subcortical gray matter volumes in relation to the surgical pain outcome. A significant group (OAp/OAr) by subcortical volume interaction was observed (**Table 2**), revealing significant differences in presurgery subcortical brain volume between postsurgical OA groups. This interaction was further studied at each factor level (subcortical brain regions) which revealed significant, uncorrected group differences in bilateral (right + left) thalamus and amygdala (**Table 3**).

Next, for each subcortical structure, we studied the influence of brain hemisphere and laterality of nociceptive input (OA site) by evaluating the interactions between OA outcome group and brain hemisphere and OA side. No significant interaction was found between group and side of OA for the thalamus and amygdala, nor a main effect of laterality (**Table 3**). For the hippocampus, there was a significant interaction between brain hemisphere and OA group that seemed to be primarily driven by a difference between groups in the left hippocampus (F [1,75] = 5.508, $P = 0.022$, mean difference [OAp-OAr: 246.392 ± 104.9 mm^3]), which did not exist for the right hippocampus (F [1,74] = 0.482, $P = 0.490$). Finally, the caudate showed a significant, uncorrected interaction between group and brain hemisphere (F [1,74] = 6.69, $P = 0.012$) and group and side of OA (F [1,74] = 5.7, $P = 0.020$). Pairwise

Table 3

Post hoc exploratory analysis for (1) each subcortical structure volume independently, (2) interaction with hemisphere (structure by osteoarthritis group by hemisphere), and (3) interaction with osteoarthritis site (structure by osteoarthritis group by laterality).

Variable	Sumsq (type III)	df	F value	P
SCv × OA group				
Thalamus	**32,664,679.52**	**1**	**2.296**	**0.009***
Group × hemisphere (L/R)	64,321.567	1	2.281	0.141
Group × OA site (CL/IL)	1055.069	1	0.032	0.859
Caudate	10,565.993	1	0.041	0.841
Group × hemisphere (L/R)	**152,182.973**	**1**	**6.684**	**0.012***
Group × OA site (CL/IL)	**133,623.114**	**1**	**5.697**	**0.020***
Putamen	67,979.195	1	0.176	0.676
Group × hemisphere (L/R)	53,151.763	1	1.158	0.222
Group × OA site (CL/IL)	44,578.387	1	1.237	0.270
Pallidum	281,081.446	1	1.409	0.239
Group × hemisphere (L/R)	16,124.086	1	1.195	0.278
Group × OA site (CL/IL)	28,457.428	1	2.070	0.154
Hippocampus	824,334.967	1	3.212	0.077
Group × hemisphere (L/R)	**296,293.344**	**1**	**4.111**	**0.046***
Group × OA site (CL/IL)	69,253.610	1	0.906	0.344
Amygdala	**361,998.612**	**1**	**4.708**	**0.033***
Group × hemisphere (L/R)	11,097.294	1	0.33	0.556
Group × OA site (CL/IL)	80,234.046	1	2.408	0.125
N. accumbens	6644.916	1	0.406	0.526
Group × hemisphere (L/R)	3929.046	1	1.066	0.305
Group × OA site (CL/IL)	99.317	1	0.025	0.875

There was a statistically significant interaction between OA group and brain subcortical volumes. Exploratory analysis showed significant volumetric differences in the thalamus ($P = 0.009$; FDR corrected 0.061) and amygdala ($P = 0.033$, FDR corrected = 0.11). A significant interaction was found between OA group and brain hemisphere for the hippocampus ($P = 0.046$, FDR corrected = 0.16) and caudate ($P = 0.022$, FDR corrected 0.08).
* $P < 0.05$.

CL, contralateral; df, degrees of freedom; FDR, false discovery rate; NIL, ipsilateral; RS, numeric rating scale; OA, osteoarthritis; OAp, osteoarthritis persisting; OAr, osteoarthritis recovering; SCv, subcortical volumes, mm^3; Sumsq, sum of squares (adjusted for age, sex, TICV, and baseline pain); TICV, total intracranial volume.

Copyright © 2023 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

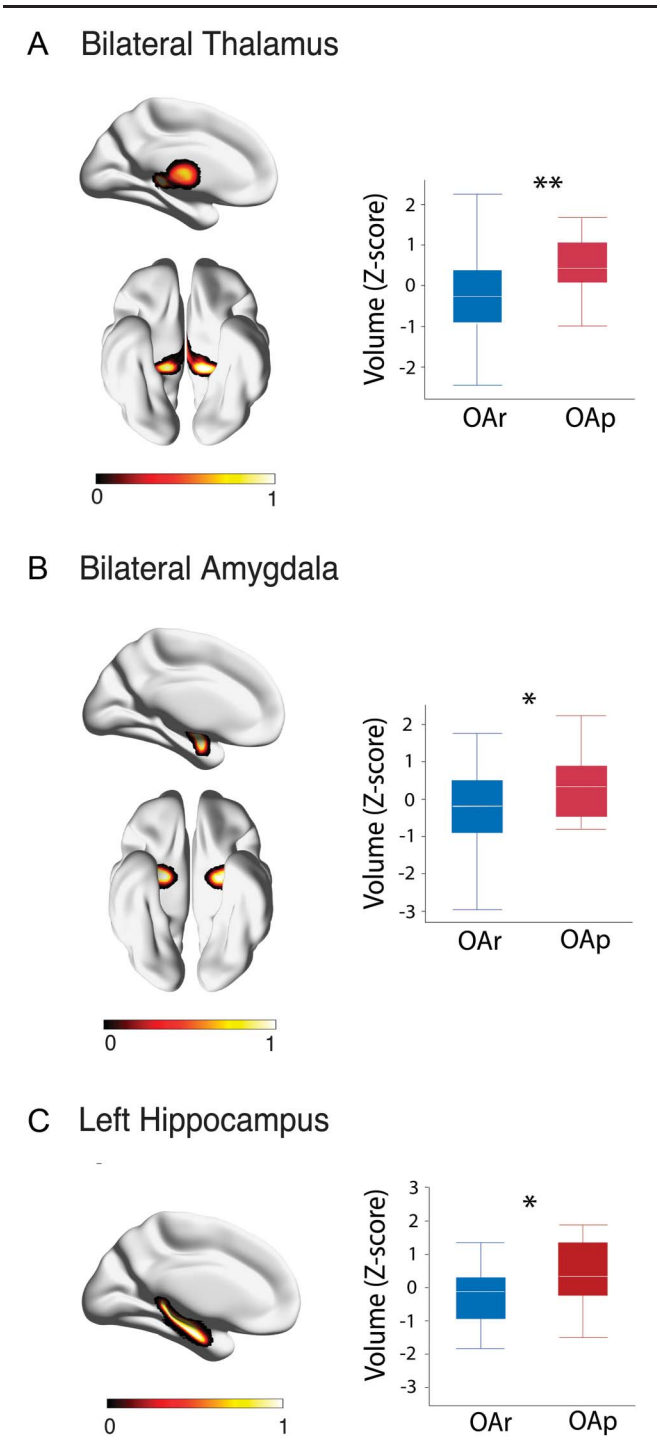

Figure 2. Preoperative subcortical volumes of the bilateral thalamus, amygdala, and left hippocampus associate with the surgical outcome (OAr and OAp) at 6 months after TKR surgery. (A–C) Boxplots show subcortical volumes per OAr and OAp groups for the bilateral thalamus, bilateral amygdala, and left hippocampus. Brain diagrams show heat maps of overlap (from 0 to 1) in the segmentation of subcortical regions across OAr and OAp groups. Subcortical volumes are projected into the cortical surface for illustration. Blue color represents the OAr group; red color represents the OAp group. $^{**}P < 0.01$; $^{*}P < 0.05$. FPR, false positive rate; OAp, osteoarthritis persisting; OAr, osteoarthritis recovering; TPR, true positive rate.

comparisons revealed no significant differences ($P \geq 0.262$) for left and right caudate, ipsilateral, and contralateral caudate between the 2 groups. This result is thus explained by a volumetric ratio difference between groups; however, absolute volumes were not distinctive between groups.

This analysis revealed that in our sample, patients who progress to persistent pain after surgery—OAp group—display larger volumes in bilateral thalamus, amygdala, and left hippocampus presurgically (**Fig. 2**).

3.4. Shape of the right anterior hippocampus and right amygdala and osteoarthritis pain persistence

After, we queried whether more granular, localized structural deformations could be associated with the surgery outcome. As shown in **Figure 3**, the right anterior hippocampus and right amygdala displayed a significant shape displacement (TFCE $P <$ 0.05, FWE-corrected for multiple comparisons). The right amygdala cluster has its statistical peak at the superficial amygdala, extending into the basolateral nucleus (subregions defined with Juelich histological atlas[1]).

The OAp group presented an outward displacement of these 2 circumscribed regions, indicating anterior hippocampal and amygdala shape extrusion was related to OA pain persistence.

3.5. Brain and clinical parameters distinct influence on postsurgery pain intensity

Next, by combining the above brain anatomical properties and clinical variables, we aimed to evaluate whether these parameters have a unique or shared contribution to pain persistence. To do so, we studied postsurgical pain as a continuous variable (NRS, 0-10) and sequentially built multiple regression models to explain its variance (**Table 4**). The first block included covariates of no interest (age, sex, TICV, and presurgery pain level) and was not statistically significant ($R^2 = 0.052$, $P = 0.391$). The second block, clinical predictors (pain duration, neuropathic scale, and anxiety level), showed a significant adjusted R^2 value of 0.306, $P < 0.001$. Adding the volumetric information (left + right) of thalamus, amygdala, and left hippocampus led to a significant R^2 change of 0.117, $P = 0.002$, for a total R^2 of 0.410, $P < 0.001$. The final model included adding the shape of the right anterior hippocampus and right amygdala (R^2 change of 0.053, $P = 0.026$, for a final R^2 of 0.455, $P < 0.001$). A post hoc linear regression analysis was conducted to evaluate the possible influence of pain duration, HADS, and DN4 in the thalamic, amygdala, and hippocampus brain volumes, and no significant associations were observed (for all structures and all clinical variables, $P > 0.3$). These results demonstrate that the predictive value of subcortical anatomic indices for postsurgical pain is additive to the clinical predictors, thus revealing singular influences.

4. Discussion

This is a longitudinal study assessing subcortical brain biomarkers of pain persistence after knee replacement surgery for OA. We have shown that presurgical subcortical brain anatomic properties, namely, the volume of bilateral thalamus, amygdala, and left hippocampus, and subregional shape alterations in the right anterior hippocampus and right amygdala associate with persistent OA pain after knee surgery. Longer pain duration, presurgical neuropathic pain, and anxiety were also predictive of pain maintenance after surgery but, importantly, the prognostic information of the constituent parameters is not redundant; rather, brain and clinical predictors account for unique influences.

Duration of OA pain, anxiety, and neuropathic pain associated with postsurgery persistent pain. Duration of OA pain having an impact on surgical outcome suggests the general concept that knee pain in time becomes more centralized, less dependent on injury-related nociceptive signaling, and thus contributes to

Copyright © 2023 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

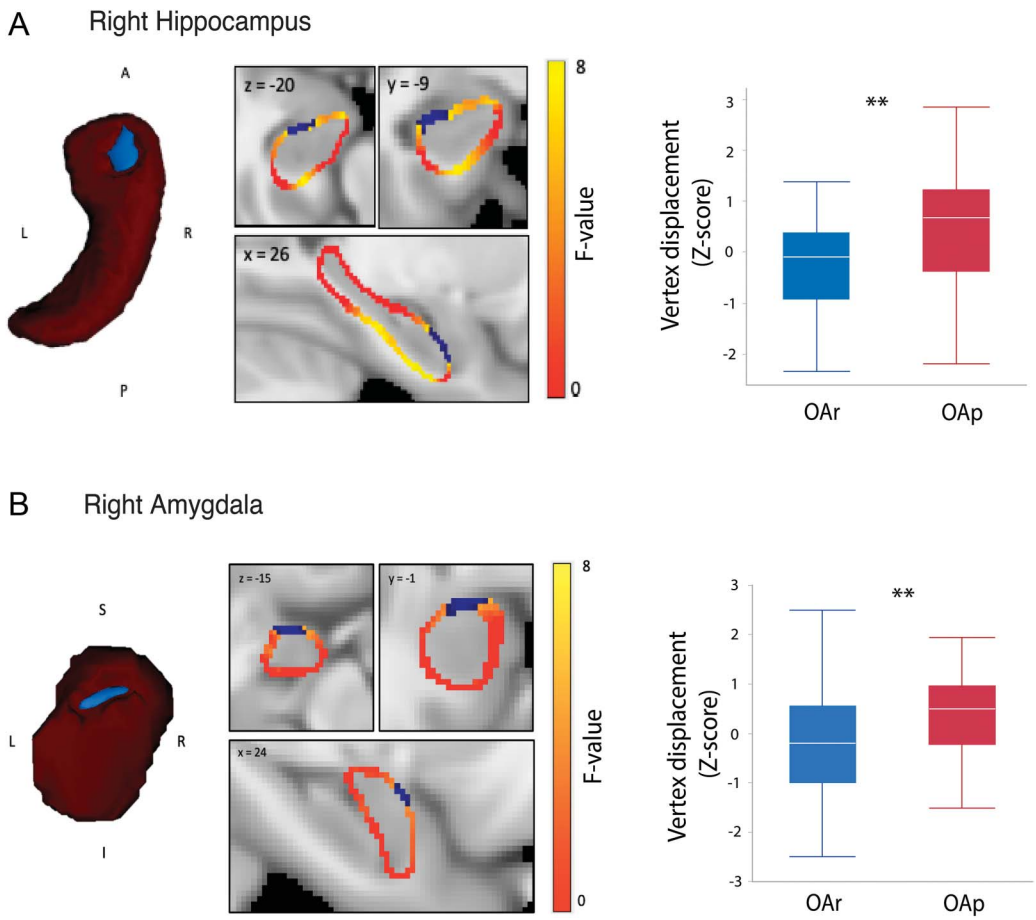

Figure 3. Preoperative shape displacements of the right amygdala and right hippocampus associate with pain persistence (OAp and OAr) 6 months after TKR surgery. (A) Right anterior hippocampal and (B) right amygdala outward displacement before surgery classifies surgical outcome (OAr and OAp). Statistics were corrected for multiple comparisons using threshold-free cluster enhancement (TFCE); blue masks displayed on the surface of the hippocampus and amygdala indicate the area with P values <0.05 after correction. Boxplot shows vertex displacement difference for the displayed clusters between OAr and OAp groups. Blue color represents the OAr group; red color represents the OAp group. $^{**}P < 0.001$. FPR, false positive rate; TKR, total knee replacement; OAp, osteoarthritis persisting; OAr, osteoarthritis recovering; TPR, true positive rate.

increased TKR failure rates. Consistent with this, previous evidence shows that brain anatomic adaptations continue to evolve for more than 10 years in patients with OA.[7] Three previous studies have considered pain duration as a factor for pain persistence after surgery; however, only one reports it as a significant factor.[7] Regarding anxiety and neuropathic pain, these traits have been reported to be associated with worse outcomes after an intervention, both for OA and other pain conditions.[16,23] A quantitative meta-analysis for predicting pain after TKR showed that most consistent parameters are baseline pain, mental health, and pain catastrophizing (Fischer $Z \leq 0.3$; corresponding to a $R^2 \leq 0.08$),[31] although anxiety has been reported as a significant factor in 1 of 7 studies. We have previously demonstrated that baseline pain is not predictive of the outcome in our sample and that anxiety and neuropathic pain belong to a larger cluster of correlated behavioral and clinical components, and such clusters were not stable across pain scales.[10] Thus, it is not surprising that in different environments diverse but correlated psychological parameters may emerge to predict TKR outcome.

Larger volumes of thalamus, amygdala, and left hippocampus were predictive of persistent pain after TKR. Partially consistent evidence has been reported in a small-sample cross-sectional study, where larger amygdala gray matter volume, as well as for nucleus accumbens and periaqueductal gray, is observed in patients with high pain vs low pain at 6 months after TKR.[32] Volumes of the amygdala and hippocampus have been identified as important risk factors for the transition from acute to chronic back pain, in which case smaller volumes were related to pain chronification.[58] Volumetric changes in these structures have also been associated with affective disorders.[38] Larger volumes of the amygdala have been associated with the severity of the depressive state in major depression[17] and with anxiety disorders.[20,57] These structures are implicated in different cognitive processes, such as emotional learning[49] and stress regulation.[48] Thus, limbic volume-related properties differentiating TKR outcomes support our proposed thesis: the same continuum of processes underly pain and negative emotional experiences.[5]

The volume of a subcortical brain structure is the integral of many properties that does not necessarily captures its complexity—subcortical structures comprised subfields with distinct neuronal populations, connectivity patterns, and functions. The shape of a subcortical region is a more granular measure than volume and may assist in the detection of localized differences in the brain structure; for instance, in Alzheimer disease, disrupted episodic memory was not driven by global atrophy but instead associated with regionally specific changes in the shape of the left hippocampus.[43] It is known that several aspects of neuroplasticity occur in adult brains (eg, dendritic arborization, synaptic remodeling, and synaptogenesis).[18] Shape deformation indices may provide relevant biological information;

Copyright © 2023 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

Table 4

Sequential regression models for pain intensity 6 months after surgery (continuous variable numeric rating scale: 0-10) using derived presurgery brain clinical and psychological measures.

Predictors	Block 1		Block2		Block 3		Block 4	
	β	*P*	B	*P*	β	*P*	B	*P*
Sex (1, female; 0, male)	0.022	0.853	−0.046	0.646	0.030	0.752	0.053	0.538
Age (y)	0.175	0.211	0.193	0.122	0.213	0.067	0.235	0.040
Baseline pain (NRS)	0.184	0.192	−0.039	0.716	−0.079	0.439	−0.097	0.333
TICV (mm^3)	0.184	0.117	0.142	0.248	0.017	0.885	0.102	0.835
DN4			0.396	0.001	0.371	0.001	0.365	0.001
HADS-A			0.284	0.013	0.314	0.004	0.307	0.004
Pain duration (y)			0.258	0.009	0.255	0.006	0.197	0.032
Thalamus L/R volume (mm^3)					0.285	0.016	0.255	0.036
Amygdala L/R volume (mm^3)					0.097	0.366	−0.035	0.783
Hippocampus L volume (mm^3)					0.058	0.626	0.108	0.918
Shape—R anterior hippocampus							0.185	0.181
Shape—R amygdala							−0.114	0.290
R^2/Adj. R^2	0.052/0.002		0.367/0.306*		0.484/0.410*		0.536/0.455*	
Δ R^2			0.314, $P < 0.001$*		0.117, $P = 0.002$†		0.053, $P = 0.026$†	

Block 1 independent variables were covariates of no interest in the analysis. Block 2 introduced clinical meaningful data for the group outcome (DN4 scale, HADS, and pain duration). Blocks 3 and 4 were significant brain properties derived from the previous analysis (volumetric properties and shape analysis results). The R^2 change between each block was significant, showing the independent and additive predictive value of clinical variables and identified subcortical brain structural variables. The beta values (β) correspond to standardized coefficients.

* $P < 0.001$

† $P < 0.05$.

DN4, Douleur Neuropathique en 4 questions; HADS, Hospital anxiety and Depression Scale; NRS, numeric rating scale; TICV, total intracranial volume.

regional abnormality patterns may reflect regional-specific atrophies and local hypertrophies.

We show patients whose pain persists after surgery presented with an outward displacement in the right anterior hippocampus and right amygdala. Concordantly, previous data from our group in chronic low back pain show an outward shape deformation in the left anterior ventral hippocampus in female patients.[45] The anterior hippocampus seems to be important in emotional and motivating behavior regulation.[50] Mutso et al.[37] studied the functional profile of the hippocampus and showed that chronic and subacute back pain are associated with larger anterior hippocampal connectivity. Their data suggest an important role for this region in the transition from acute to chronic pain and in the pathophysiology of chronic pain, possibly reflecting learning and emotional deficits seen in chronic pain.

Altered amygdala shape has been associated with different conditions, namely, with panic disorder,[61] and the severity of PTSD post-traumatic stress disorder symptoms (right amygdala).[27] In our data, we show that the right amygdala presented an outward displacement from the mean surface in patients with persistent pain. Importantly, it was previously shown in an animal model of OA that there is a right hemispheric lateralization of pain processing in the amygdala.[24] The right amygdala is known to have a predominant role in negative emotions.[62] Hemisphere lateralization of amygdala shape changes in persistent pain subjects is thus consistent with the negative emotional–affective component of chronic pain.[24] In sum, our data show that individuals more prone to continue experiencing pain after TKR display specific outward displacement of the anterior right hippocampus and right amygdala, which are involved in emotional and cognitive regulation of memory and emotional processes.

The thalamus has a central role in processing information related to pain; it is a relay of ascending nociceptive information and is associated with both sensory discriminative and affective motivational components of pain.[3] We observed bilateral involvement of this region. If we had observed solely a contralateral adjustment, it would suggest somatic lateral thalamic nociceptive signaling involvement. The bilaterality instead suggests engagement of medial thalamic affective circuitry, perhaps providing a direct route to pain-associated affect integration to the hippocampus and amygdala. Gwilym et al.[21] showed that patients with hip OA have smaller thalamus grey matter volumes than healthy subjects, and these thalamic volume differences reverse after hip arthroplasty and concomitant decreases in pain. At this point, we do not know whether the volumetric changes are reversible in our sample.

The directionality of volumetric outcomes warrants further discussion. Patients with OA live with ongoing pain for months, years, or even decades. Central adaptations secondary to persistent nociceptive stimuli can occur because of the long-lasting pain—continuous barrage of nociceptive signaling—resulting in adaptive or maladaptive plasticity, beyond that observed in subacute pain models. In addition, the equally long-lasting affective and emotional toll of pain, and the stress of living in pain, may further affect the differences in thalamus, hippocampus, and amygdala anatomy between patients with OAp or OAr. On the other hand, the evolution of pain after TKR surgery is complex: how much of the pain after TKR reflects the presurgical pain? How much of the pain is induced by the surgical aggression? The cross-sectional study of OA brain biomarkers prevents us to disentangle biomarkers that arise with and reflect the status of the disorder from a priori traits conditioning the outcome of the disease. Further study of brain changes postsurgically is warranted.

We uncovered brain anatomical and clinical variables that capture pain after surgery. It is critical to understand whether brain biomarkers and clinical variables are associated in explaining the surgical outcome. By applying sequentially model blocks or groups of variables, we demonstrated that brain anatomical

Copyright © 2023 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

and clinical variables are additive in explaining the outcome and thus not interchangeable. A longer period living with the stress of chronic pain and the sensory nociceptive drive may lead to the emergence of a neuropathic pain profile and higher levels of anxiety. At the same time, primary brain properties associated with trait anxiety and a neuropathic pain profile from onset may lead to a persistent pain state. These concepts remain to be disentangled, and finding clinical brain correlates are of uttermost importance in the future.

The present work has limitations that should be acknowledged. It is an observational longitudinal study. Thus, although the obtained results could be considered causal mechanistic insights of biological processes that underlie pain persistence after knee surgery, it is important to highlight that our study is one of the first of its kind and given its exploratory nature, it requires further validation and replication. We do not control for multiplicity of tests of our post hoc analysis; from this perspective, our post hoc analysis should be seen as preliminary and replication analysis should follow. Finally, we only evaluated structural properties of subcortical brain areas; the study of functional properties and anatomic connectivity besides the study of cortical brain properties is of high importance and will be performed in continuity of this study.

Current notions of persistent pain after a technically successful TKR surgery have focused on peripheral and spinal cord sensitization, abnormal descending pain modulation, or clinical and psychological dimensions, without a clear mechanistic link to pain physiology. We have shown that structural properties of the brain's limbic circuitry—particularly the amygdala, hippocampus, together with the thalamus—associate with pain persistence after TKR surgery. These results support the importance of limbic neuroanatomical factors in the persistence of chronic pain and open a new avenue not only for studying postsurgery pain mechanisms but also in clinical care and management of patients with OA pain.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgments

The authors thank to Dr. Paulo Oliveira for the clinical support and supervision of patients enrolled in the study and all the members of the orthopedic department of Centro Hospitalar Universitário de São João, Porto, for their support with data collection. The authors thank to Unilabs Boavista and Dr. Nuno Martins for all the support in imaging data acquisition. The authors are thankful to all Apkarian laboratory and Galhardo laboratory members who contributed to this study with their time and resources.
J. Barroso was funded through CCDRN [Norte-08-5369-FSE-000026], OARSI Collaborative Scholarship 2018, and Luso-American Development Foundation R&D@PhD scholarship grant. Neuroimage data acquisition was provided by Unilabs Boavista and the Grünenthal Young Pain Researcher 2017 Grant.

Article history:
Received 14 September 2022
Received in revised form 9 February 2023
Accepted 2 April 2023
Available online 13 July 2023

References

[1] Amunts K, Kedo O, Kindler M, Pieperhoff P, Mohlberg H, Shah NJ, Habel U, Schneider F, Zilles K. Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps. Anat Embryol (Berl) 2005;210:343–52.
[2] Andersen LØ, Gaarn-Larsen L, Kristensen BB, Husted H, Otte KS, Kehlet H. Subacute pain and function after fast-track hip and knee arthroplasty. Anaesthesia 2009;64:508–13.
[3] Apkarian AV, Shi T, Brüggemann J, Airapetian LR. Segregation of nociceptive and non-nociceptive networks in the squirrel monkey somatosensory thalamus. J Neurophysiol 2000;84:484–94.
[4] Baert IAC, Lluch E, Mulder T, Nijs J, Noten S, Meeus M. Does pre-surgical central modulation of pain influence outcome after total knee replacement? A systematic review. Osteoarthritis Cartilage 2016;24:213–23.
[5] Baliki MN, Apkarian AV. Nociception, pain, negative moods, and behavior selection. Neuron 2015;87:474–91.
[6] Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat Neurosci 2012;15:1117–9.
[7] Baliki MN, Schnitzer TJ, Bauer WR, Apkarian AV. Brain morphological signatures for chronic pain. PLoS One 2011;6:e26010.
[8] Barroso J, Branco P, Apkarian AV. Brain mechanisms of chronic pain: critical role of translational approach. Transl Res 2021;238:76–89.
[9] Barroso J, Vigotsky AD, Branco P, Reis AM, Schnitzer TJ, Galhardo V, Apkarian AV. Brain gray matter abnormalities in osteoarthritis pain: a cross-sectional evaluation. PAIN 2020;161:2167–78.
[10] Barroso J, Wakaizumi K, Reckziegel D, Pinto-Ramos J, Schnitzer T, Galhardo V, Apkarian AV. Prognostics for pain in osteoarthritis: do clinical measures predict pain after total joint replacement? PLoS One 2020;15:e0222370.
[11] Barroso J, Wakaizumi K, Reis AM, Baliki M, Schnitzer TJ, Galhardo V, Apkarian AV. Reorganization of functional brain network architecture in chronic osteoarthritis pain. Hum Brain Mapp 2020;4:1206-22.
[12] Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol 1995;57:289–300.
[13] Beswick AD, Wylde V, Gooberman-Hill R. Interventions for the prediction and management of chronic postsurgical pain after total knee replacement: systematic review of randomised controlled trials. BMJ Open 2015;5:e007387.
[14] Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open 2012;2:e000435.
[15] Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lantéri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). PAIN 2005;114:29–36.
[16] Fletcher D, Stamer UM, Pogatzki-Zahn E, Zaslansky R, Tanase NV, Perruchoud C, Kranke P, Komann M, Lehman T, Meissner W. Chronic postsurgical pain in Europe: an observational study. Eur J Anaesthesiol 2015;32:725–34.
[17] Frodl T, Meisenzahl E, Zetzsche T, Bottlender R, Born C, Groll C, Jäger M, Leinsinger G, Hahn K, Möller H-J. Enlargement of the amygdala in patients with a first episode of major depression. Biol Psychiatry 2002;51:708–14.
[18] Gage FH. Structural plasticity of the adult brain. Dialogues Clin Neurosci 2004;6:135–41.
[19] Gonçalves RS, Cabri J, Pinheiro JP, Ferreira PL. Cross-cultural adaptation and validation of the Portuguese version of the knee injury and osteoarthritis outcome score (KOOS). Osteoarthritis Cartilage 2009;17:1156–62.
[20] Günther V, Ihme K, Kersting A, Hoffmann K-T, Lobsien D, Suslow T. Volumetric associations between amygdala, nucleus accumbens, and socially anxious tendencies in healthy women. Neuroscience 2018;374:25–32.
[21] Gwilym SE, Filippini N, Douaud G, Carr AJ, Tracey I. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based morphometric study. Arthritis Rheum 2010;62:2930–40.
[22] HCUP fast stats. Healthcare cost and utilization project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality, 2021. Available at: www.hcup-us.ahrq.gov/faststats/national/inpatientcommonprocedures.jsp? Accessed July 23, 2021.
[23] Hochman JR, Gagliese L, Davis AM, Hawker GA. Neuropathic pain symptoms in a community knee OA cohort. Osteoarthritis Cartilage 2011;19:647–54.
[24] Ji G, Neugebauer V. Hemispheric lateralization of pain processing by amygdala neurons. J Neurophysiol 2009;102:2253–64.

Copyright © 2023 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

[25] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
[26] Kim DH, Pearson-Chauhan KM, McCarthy RJ, Buvanendran A. Predictive factors for developing chronic pain after total knee arthroplasty. J Arthroplasty 2018;33:3372–8.
[27] Klaming R, Spadoni AD, Veltman DJ, Simmons AN. Expansion of hippocampal and amygdala shape in posttraumatic stress and early life stress. Neuroimage Clin 2019;24:101982.
[28] Knoop J, Steultjens MPM, van der Leeden M, van der Esch M, Thorstensson CA, Roorda LD, Lems WF, Dekker J. Proprioception in knee osteoarthritis: a narrative review. Osteoarthritis Cartilage 2011;19: 381–8.
[29] Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg 2007;89:780–5.
[30] Lahtinen P, Kokki H, Hynynen M. Pain after cardiac surgery. Anesthesiology 2006;105:794–800.
[31] Lewis GN, Rice DA, McNair PJ, Kluger M. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. Br J Anaesth 2015;114:551–61.
[32] Lewis GN, Wartolowska KA, Parker RS, Sharma S, Rice DA, Kluger M, McNair PJ. A higher grey matter density in the amygdala and midbrain is associated with persistent pain following total knee arthroplasty. Pain Med 2020;21:3393–400.
[33] Maiese K. Picking a bone with WISP1 (CCN4): new strategies against degenerative joint disease. J Transl Sci 2016;1:83–85.
[34] Malfait A-M, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. Nat Rev Rheumatol 2013;9:654–64.
[35] Mansour A, Baria AT, Tetreault P, Vachon-Presseau E, Chang P-C, Huang L, Apkarian AV, Baliki MN. Global disruption of degree rank order: a hallmark of chronic pain. Sci Rep 2016;6:34853.
[36] Mao CP, Bai ZL, Zhang XN, Zhang QJ, Zhang L. Abnormal subcortical brain morphology in patients with knee osteoarthritis: a cross-sectional study. Front Aging Neurosci 2016;8:3.
[37] Mutso AA, Radzicki D, Baliki MN, Huang L, Banisadr G, Centeno MV, Radulovic J, Martina M, Miller RJ, Apkarian AV. Abnormalities in hippocampal functioning with persistent pain. J Neurosci 2012;32: 5747–56.
[38] Nolan M, Roman E, Nasa A, Levins KJ, O'Hanlon E, O'Keane V, Willian Roddy D. Hippocampal and amygdalar volume changes in major depressive disorder: a targeted review and focus on stress. Chronic Stress 2020;4:247054702094455.
[39] Nugent AC, Luckenbaugh DA, Wood SE, Bogers W, Zarate CA, Drevets WC. Automated subcortical segmentation using FIRST: test-retest reliability, interscanner reliability, and comparison to manual segmentation: reliability of automated segmentation using FIRST. Hum Brain Mapp 2013;34:2313–29.
[40] Pais-Ribeiro J, Silva I, Ferreira T, Martins A, Meneses R, Baltar M. Validation study of a Portuguese version of the hospital anxiety and depression scale. Psychol Health Med 2007;12:225–35, quiz 235–7.
[41] Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 2011;56:907–22.
[42] Pereira D, Peleteiro B, Araújo J, Branco J, Santos RA, Ramos E. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. Osteoarthritis Cartilage 2011;19:1270–85.
[43] Thomann PA, Seidl U, Brinkmann J, Hirjak D, Traeger T, Christian Wolf R, Essig M, Schrode J. Hippocampal morphology and autobiographic memory in mild cognitive impairment and Alzheimer's disease. Curr Alzheimer Res 2012;9:507–15.
[44] Podsiadlo D, Richardson S. The timed "up & go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39:142–8.
[45] Reckziegel D, Abdullah T, Wu B, Wu B, Huang L, Schnitzer TJ, Apkarian AV. Hippocampus shape deformation: a potential diagnostic biomarker for chronic back pain in women. PAIN 2020;162:1457–67.
[46] Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Arthritis Rheum 2000;43: 1905–15.
[47] Rejeski WJ, Ettinger WH, Schumaker S, James P, Burns R, Elam JT. Assessing performance-related disability in patients with knee osteoarthritis. Osteoarthritis Cartilage 1995;3:157–67.
[48] Ressler KJ. Amygdala activity, fear, and anxiety: modulation by stress. Biol Psychiatry 2010;67:1117–9.
[49] Richter-Levin G. The amygdala, the hippocampus, and emotional modulation of memory. Neuroscientist 2004;10:31–9.
[50] Sahay A, Hen R. Adult hippocampal neurogenesis in depression. Nat Neurosci 2007;10:1110–5.
[51] Singh JA, Gabriel S, Lewallen D. The impact of gender, age, and preoperative pain severity on pain after TKA. Clin Orthop 2008;466: 2717–23.
[52] Singh JA, Yu S, Chen L, Cleveland JD. Rates of total joint replacement in the United States: future projections to 2020–2040 using the national inpatient sample. J Rheumatol 2019;46:1134–40.
[53] Smith S, Nichols T. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. NeuroImage 2009;44:83–98.
[54] Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, De Stefano N. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 2002;17:479–89.
[55] Stanton TR, Lin C-WC, Smeets RJEM, Taylor D, Law R, Lorimer Moseley G. Spatially defined disruption of motor imagery performance in people with osteoarthritis. Rheumatology 2012;51:1455–64.
[56] Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychol Assess 1995;7:524–32.
[57] Suor JH, Jimmy J, Monk CS, Phan KL, Burkhouse KL. Parsing differences in amygdala volume among individuals with and without social and generalized anxiety disorders across the lifespan. J Psychiatr Res 2020;128:83–9.
[58] Vachon-Presseau E, Tétreault P, Petre B, Huang L, Berger SE, Torbey S, Baria AT, Mansour AR, Hashmi JA, Griffith JW, Comasco E, Schnitzer TJ, Baliki MN, Apkarian AV. Corticolimbic anatomical characteristics predetermine risk for chronic pain. Brain 2016;139:1958–70.
[59] Woolhead GM, Donovan JL, Dieppe PA. Outcomes of total knee replacement: a qualitative study. Rheumatology 2005;44:1032–7.
[60] Wylde V, Palmer S, Learmonth ID, Dieppe P. The association between pre-operative pain sensitisation and chronic pain after knee replacement: an exploratory study. Osteoarthritis Cartilage 2013;21:1253–6.
[61] Yoon S, Kim JE, Kim GH, Kang HJ, Kim BR, Jeon S, Im JJ, Hyun H, Moon S, Lim SM, Lyoo IK. Subregional shape alterations in the amygdala in patients with panic disorder. PLoS One 2016;11:e0157856.
[62] Yoshimura S, Ueda K, Suzuki S, Onoda K, Okamoto Y, Yamawaki S. Self-referential processing of negative stimuli within the ventral anterior cingulate gyrus and right amygdala. Brain Cogn 2009;69:218–25.

Copyright © 2023 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.