Tapentadol effects on brain response to pain in sensitized patients with knee osteoarthritis

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Running title: Tapentadol and brain response to pain

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Abstract

Objective: Pain sensitization, in the form of knee tenderness and anatomically spread hyperalgesia, is notably common in patients with knee osteoarthritis and is often refractory to conventional interventions. Tapentadol, as an opioid receptor agonist and noradrenaline reuptake inhibitor, has been proposed as a potentially effective symptomatic treatment for pain-sensitized osteoarthritis patients. We empirically tested whether tapentadol could attenuate brain response to painful stimulation on the tender knee using functional MRI.

Methods: Pressure painful stimulation was applied to the articular interline and the tibial surface, a commonly sensitized site surrounding the joint. Thirty patients completed the crossover trial designed to compare prolonged release tapentadol and placebo effects administered over 14 days.

Results: We found no effects in the direction of the prediction. Instead, patients administered with tapentadol showed stronger activation in response to pressure on the tender site in the right prefrontal cortex and somatosensory cortices. The somatosensory effect was compatible with the spread of neural activation around the knee cortical representation. Consistent with the functional MRI findings, the patients showed higher clinical ratings of pain sensitization under tapentadol and a significant positive association was identified between the number of tapentadol tablets and the evoked subjective pain.

Conclusion: The tapentadol effect paradoxically involved both the spread of the somatosensory cortex response and a stronger activation in prefrontal areas with a recognized role in the appraisal of pain sensations. Further studies are warranted to explore how osteoarthritis patients may benefit from powerful analgesic drugs without the associated risks of prolonged use. EudraCT-[2016-005082-31].

Keywords: Osteoarthritis, Functional MRI, brain activation, pain sensitization, opioids, sensory cortex.

Key messages:

The study informs on opioid-related pain sensitization

We found stronger brain activation in response to pressure on the knee tender site

This functional MRI study illustrates how opioids may paradoxically sensitize to pain

Introduction

Refractory, disabling pain is frequently associated with central nervous system (CNS) sensitization, which involves a variety of pathophysiological phenomena increasing the excitability of nociceptive pathways. Pain sensitization is manifested as pain hypersensitivity with anatomically spread hyperalgesia and enhanced temporal summation of pain following repeated stimulation (1). Pain sensitization is common in chronic knee osteoarthritis (OA) patients (2). In a previous study by our group (3), 55% of OA patients showed some evidence of pain sensitization and it was considered clinically severe in 32%.

In this context, the potential clinical benefits of drugs capable of targeting these levels of nociceptive processing are well worth exploring. Tapentadol, as a μ-opioid receptor agonist and noradrenaline reuptake inhibitor, *a priori* is a privileged treatment agent for pain central sensitization as it may interfere with the transmission and processing of nociceptive information at various points in the CNS; it would also activate the descending inhibitory projections at the supraspinal level (4-6). However, a paradoxically opposite effect of pain sensitization has been described for the use of drugs with opioid action (7,8). Therefore, the suitability of tapentadol for the prolonged treatment of pain-sensitized OA patients should optimally be tested in an empirical manner.

A limitation in testing treatments is partly related to the inherent subjectivity and variability of pain ratings. Consequently, there is significant interest in developing objective measures of the analgesic effect. One potential option is the use of brain imaging techniques such as functional MRI (fMRI), which may comprehensively assess neural activity related to the variety of dimensions associated with the pain experience (3,9-11).

We have used fMRI to specifically assess the effects of tapentadol on brain response to painful stimulation in knee OA patients with clinical evidence of pain sensitization. Pressure stimuli were separately applied to the painful knee at the articular interline (test 1) and at the superior tibial surface, a commonly sensitized site surrounding the joint (test 2). Our primary objective was to compare placebo and tapentadol effects on pain-evoked brain activity (primary outcome measure). We hypothesized that tapentadol would attenuate such a brain response compared with placebo. In addition, based on the opportunity of characterizing a diversity of pain dimensions, we explored whether the imaging approach could contribute to elucidating potential action mechanisms of the hypothesized effects on pain sensitization.

Methods

Overview of study design

The study was a double-blind, randomized, placebo-controlled, 3-phase crossover trial. After a screening visit, patients participated in three treatment conditions; tapentadol, placebo and no treatment, at the end of which an fMRI exam was administered in each case. The rationale for including a non-treatment condition was to enable estimation of the placebo effect as a reference. The duration of each treatment phase was 14 days and the time between treatments was 14-21 days. The order of the treatment phases was randomized. Independent pharmacists dispensed the compounds to the investigator according to a randomization list, while the investigators and the patients were constantly kept blind to the treatment assignment.

Study population

Participants were recruited by Rheumatology researchers from a referral OA Unit at the Hospital del Mar, Barcelona, in 2019 and 2020. The study was conducted in accordance with

the principles expressed in the Declaration of Helsinki and was approved by the Ethical Committee of Clinical Research of the Parc de Salut Mar, Barcelona (ref. MP-TAP-2016-01) and the Spanish Agency of Medicine and Sanitary Products (ref. MUH/CLIN/EC). All patients provided written informed consent. The trial was designed according to CONSORT recommendations (12) and was registered in the EudraCT (European Union Drug Regulating Authorities Clinical Trials) database, identifier number 2016-005082-31, title; *Assessment of tapentadol effects on patients with pain central sensitization using functional MRI*.

Eligibility criteria. A patient was eligible for inclusion if the following criteria applied: Radiological and clinical diagnosis of knee OA based upon American College of Rheumatology (13) criteria. Pain sensitization affecting the knee defined by combining clinical and experimental (pain thresholds) evidence. Patients with Brief Pain Inventory (14) item 5 score of 6-10 points at screening. Subjects either male or female and at least 45 years of age who could be treated in accordance with the technical specifications of summary of product characteristics (SmPC).

Patients were not eligible if they were female with childbearing potential, showed body weight >120kg (a restriction for MRI), had severe or non-stable medical conditions, or showed prior intolerance to opioids. Treatments not allowed were analgesic and anti-inflammatory drugs (3 days), injections in the joint or muscle (3 months), tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (as a recent, < 6 weeks, prescription) and monoamine oxidase inhibitors. Subjects were not permitted to exercise heavily for 12 hours prior to fMRI assessment.

Rescue medication (paracetamol 1g/8h) was allowed, but was withdrawn for a minimum of 24 h prior to the fMRI assessment. Subjects could take their chronic (non-analgesic and non-anti-inflammatory) medication if the treatments had been followed continuously for at least six weeks prior to assessment.

Drug dosage

Patients received a tailored oral dose of prolonged release tapentadol hydrochloride for 14 consecutive days before the fMRI session and placebo with an identical regime and appearance before the corresponding fMRI session. Flexible dose tailoring (titration) started with an evening dose of 50 mg, which was increased in successive steps up to 250 mg a day if tolerability was good (Supplementary Table 1).

Randomization

Patients were assigned to one of the six possible treatment sequences in accordance with a randomization schedule (A/B/C; A/C/B; B/A/C; B/C/A; C/A/B; C/B/A. A: tapentadol, B: placebo, C: no treatment) with an equal allocation ratio (1:1:1:1:1:1). The randomization scheme was generated through the website Randomization.com ⟨http://www.randomization.com⟩ using the second generator, which creates random permutations of treatments for situations in which subjects receive all the treatments in random order. The system generated a unique number for each randomized patient and the randomization schedule was stratified in blocks of 12. A single independent researcher was aware of the randomization information (LBH).

Sample size

There is no consensus as to sample size estimation for fMRI studies. Empirical experiments have demonstrated that a number above 24 subjects is optimal to achieve 80% power for a threshold of 0.05 in conventional task activation experiments (15).

Clinical assessments

Screening assessments included complete medical history, physical examination, ECG, X-ray of the knee and an inclusion/exclusion criteria checklist. At screening, the knee, right or left, to be stimulated during fMRI was selected based on the most symptomatic side. Potential candidates were fully briefed on the study. If they agreed to participate, they duly signed the informed consent and were assigned a unique study number.

Patients were clinically and experimentally evaluated on the last day of each treatment phase prior to the fMRI session, which always took place in the afternoon, following the final morning dose. The severity of pain sensitization was evaluated by means of a Pain Sensitization Global Score combining the ratings of (i) clinical pain intensity, (ii) clinical pain spreading, (iii) number of tender points and (iv) pain temporal summation. To compute such a Pain Sensitization Global Score, the values of the four ratings, scaled each to 0-10 points, were added to provide a single score ranging from 0-40.

The assessment of **clinical pain intensity** was based on items 3-to-6 of the Brief Pain Inventory (14), which rate mechanical pain (mean, maximum and minimum) in the preceding 24h and current pain using 11-point numerical rating scales (NRS) (ranging from 0, no pain, to 10, the most severe pain). Four ratings in total and maximum score of 40.

Pain spreading was clinically evaluated by manual palpation of the knee and surrounding areas. A highly trained experimenter (GMV) rated the severity of pain verbally and non-verbally expressed by the patient as mild (score 2), moderate (score 4) and severe (score 6). Severe pain was given a score of 5 if it did not exceed half of the area examined, a score of 3 similarly for non-extensive moderate pain and a score of 1 for non-extensive mild pain.

The **number of tender points** was experimentally determined. A custom-made MRI compatible pressure algometer was used (3) to measure *pressure pain thresholds*. The probe ($1cm^2$) was placed perpendicular to the selected anatomical sites and pressure was applied (30 kPa/s) until the participant defined the pressure as pain. Pressure pain thresholds were measured twice on each site of the extended Arendt-Nielsen peripatellar map (3,16,17) (Supplementary Figure 1) and the mean of both measures was used.

Temporal summation to repeated pressure painful stimulation was assessed on the anterior/medial tibial surface, which was one of the sites to be stimulated during fMRI. The sequential stimulation consisted of 10 pressure stimuli (1s duration and 1s interval) applied with the algometer at the pressure pain threshold level (16). The subjects rated pain intensity for the first and last stimuli with an 11-point NRS.

Additional clinical assessments to characterize the patient sample included: The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical-function scale (18). PainDETECT questionnaire (19). An 11-point rating of spontaneous, resting subjective pain perceived in the whole body, as a measure of primary, fibromyalgia-like pain sensitization. An 11-point pain rating generated with a pressure of $4kg/cm^2$ during 2s on the tibial surface, as an estimation of regional pain sensitization. The Hospital Anxiety and Depression Scale (HADS) (20,21).

Functional MRI testing stimuli

Test 1 involved pressure stimulation on the medial articular interline of the selected knee and Test 2 pressure stimulation on the anterior surface of the tibial region. Complete description of the adopted procedures is reported in Supplementary Material and Supplementary Figure 2.

Functional MRI

Details on fMRI acquisition, preprocessing and the control of potential head motion effects are provided in Supplementary Material. The study included 2 fMRI sequences; Knee Articular Interline test and Tibial Surface test, with identical block paradigm alternating 11 baseline periods of 20 seconds (plus a final baseline period of 30 seconds) and 11 painful stimulation periods of 10 seconds (total six minutes) (Supplementary Figure 2).

Functional MRI analysis

First-level (single-subject) analysis. The fMRI signal response at each voxel was modelled using study-specific regressors adjusted to the actual brain response to our pressure stimulation. In previous studies of independent samples using similar stimuli, temporal analyses demonstrated that blocks of 10s of pressure stimulation generating pain of moderate (5-7/10) intensity evoke a brain response lasting about 16s (3,10,22). Subjective pain was perceived with a duration similar to brain activation (22). Therefore, we modelled brain activation with a boxcar regressor considering 11 activation blocks of 16s and applying a hemodynamic delay of 4s (Supplementary Figure 2). Brain activation (primary outcome measure) was estimated based on the SPM contrast “resting blocks < pressure blocks”.

Group-level analysis. The resulting first-level SPM contrast images were carried forward to group-level analyses. Paired t-tests were used to compare brain activity evoked during tapentadol and placebo conditions (primary analysis) including data from 30 patients in the interline analysis and 29 patients in the tibial analysis. In addition, each intervention was compared with the no-treatment condition. One-sample t-test designs were used to generate group activation maps. In this case, the groups included an identical number of subjects (i.e., patients with data from the three conditions) to make the maps comparable upon visual

inspection (n=29 for the interline test and n=27 for the tibial test). In addition, voxel-wise linear regression was used to test the association between the number of tablets taken and evoked brain activity.

As the hemisphere (right or left) activated at the primary and second somatosensory cortices depends on the body side (left or right) stimulated, a sub-analysis was conducted using right-to-left flipped images for the 14 patients stimulated on their left knee and original (non-flipped) images for the 16 patients stimulated on their right knee.

In all analyses, results were considered significant when clusters formed at a threshold of $p< 0.005$ survived whole-brain family-wise error (FWE) correction ($p< 0.05$), calculated by means of SPM. SPM set level-corrected whole-brain results were also considered to provide a more complete characterization of changes at the pain network level.

The statistical analysis of **behavioral data** involved paired t-tests and Pearson's correlations.

Results

Thirty patients were finally deemed valid for the primary study analysis involving the assessment of tapentadol treatment effects compared with placebo. Supplementary Figure 3 details the participant Flow Diagram. Table 1 reports the clinical characteristics of the sample. The final dose (last day) of tapentadol was 250 mg a day (step 4) in all but 3 patients.

Intervention effects on subjective pain sensitization measures

We were unable to demonstrate a positive, relieving effect of tapentadol. Instead, patients under the placebo condition showed a significantly higher reduction in pain sensitization compared to tapentadol. Pain Sensitization Global Score showed a mean (±SD) of 16.5 (±6.1)

points under tapentadol treatment and 14.0 (±6.4) under placebo (t=3.0 and p=0.006). Table 2 summarizes the results of the pain sensitization measure analysis.

Intervention effects on subjective pain evoked during fMRI testing

Similarly, tapentadol did not attenuate pain generated by knee interline and tibial surface stimulation during the fMRI experiments (Supplementary Table 2). In contrast, a significant association (r=0.54; p=0.002) was observed between the number of tapentadol tablets taken during the whole treatment period and subjective pain perceived when applying pressure on the tibial surface (Supplementary Figure 4). A sub-analysis excluding the patients who took a low dose (20 tablets or less) indicates that the association tended to involve other sensitization measures (Supplementary Table 3). The number of placebo tablets did not correlate with any measure of pain.

Functional MRI Results

Knee articular interline test

Figure 1 shows 3D brain images illustrating one-sample t-tests results for the three study conditions and Supplementary Figure 5 shows representative orthogonal views. There was no apparent reduction of brain activation during knee interline stimulation under tapentadol treatment compared with placebo. Paired comparisons showed only one significant effect in the knee articular interline analysis. Significant neural activation reduction was identified under placebo compared with no treatment in the paracentral lobule involving the somatosensory area at the cortical representation of the lower limb (Supplementary Figure 6 and Supplementary Table 4).

Tibial surface test

Figure 2 similarly presents 3D images to illustrate one-sample t-tests results for this analysis (see also Supplementary Figure 5). There was an apparent enhancement of brain activation

during tibial surface stimulation under tapentadol treatment compared with the other conditions upon visual inspection. Paired t-tests confirmed significant effects in this analysis in the form of stronger activation under tapentadol compared with placebo in the paracentral lobule and right dorsal prefrontal cortex (Figure 3 and Supplementary Table 4). No association was found between the number of tapentadol tablets and brain activation.

A sub-analysis was conducted using flipped images in patients with affected left knees (and non-flipped images for right knee cases) to evaluate the lateralized effects in the somatosensory cortices and closely related regions (motor and supplementary areas). Supplementary Figure 7 illustrates one-sample t-test results for patients with complete tibial test data for the three conditions. This analysis showed the most demonstrative results of tapentadol's effects on the sensory areas. Figure 4 illustrates the results obtained by comparing tapentadol and placebo conditions in the flipped sub-analysis. Significantly higher activation was identified under tapentadol in the primary somatosensory cortex ipsilateral (and not contralateral) to the stimulated knee (Supplementary Table 4). A similar effect was also identified in the ipsilateral second somatosensory area (parietal operculum), paracentral lobule, superior parietal cortex and premotor cortex. Such an anatomical pattern expresses a cortical spreading of neural activation, which is consistent with the observed spreading of painful, tender areas around the knee.

Figure 4 additionally shows the activation reduction effect of placebo compared with no treatment in the articular interline test analysis using flipped images. In this case, significant differences were identified in the paracentral lobule with a lateralized effect extending to the somatosensory cortex contralateral to the stimulated knee (Supplementary Table 4). Contralateral activations are expected due to sensory pathway decussation.

A further analysis revealed that the cortical activation spreading by tapentadol may in part express reduced neural inhibition. Indeed, Supplementary Figure 8 shows group one-sample results for the contrast “activation condition (pressure on) < resting condition (pressure off)” at a low threshold ($p<0.05$), which identifies neural areas inhibited during painful stimulation in the tibial test analysis using flipped images. The model shows that inhibited areas in the placebo condition involved the ipsilateral (and not the contralateral) primary somatosensory cortex and surrounding ipsilateral and contralateral cortices. Such a pattern of neural inhibition was not evident in the tapentadol condition map.

Discussion

We have empirically tested whether a treatment agent with dual opioid and noradrenergic action such as tapentadol could attenuate the brain response to pain in sensitized patients with knee OA. We found no effect in the direction of the prediction. Instead, patients under tapentadol showed stronger activation in response to knee painful stimulation in the right prefrontal cortex and somatosensory cortices compared with placebo. The effect was more evident when applying pressure stimuli on the tibial surface, which more accurately represents the sensitized component of knee pain. A significant positive association was identified between the number of tapentadol tablets taken and subjective pain evoked during tibial surface stimulation. The fMRI findings were consistent with the drug effect on clinical measures of pain sensitization showing a significant increase in severity under tapentadol.

fMRI allows us to identify neural activity related to different aspects of the composite pain experience from the primary sensory processing to the ultimate individual appraisal of the perceived sensation (23). We found tapentadol-related effects at both extremes of the brain’s response to pain. Indeed, significant changes involved the right prefrontal lobe, which deals

with the highest-order processing of noxious stimuli by coding stimulus intensity, unpleasantness and potential danger (22,24), and the somatosensory cortices that contribute to pain experience by coding the body site and sensory quality of the stimulus (25).

The results at the sensory level indicate that the tapentadol effect may be related to the cortical spreading of neural changes around the cortical representation of the knee. That is, instead of reduced activity in the knee's primary cortex associated with the placebo effect, tapentadol was associated with stronger activation in primary and second somatosensory areas ipsilateral to the stimulated knee and sensorimotor areas surrounding its cortical representation. Such spatial spreading of the cortical sensory response to pressure stimulation is consistent with the observed spread of painful, tender areas around the knee. The analysis of brain deactivations suggests that reduced inhibition may contribute to the augmented cortical response.

Our results further expose a paradox in medicine implying that the most powerful analgesic drugs may ultimately sensitize the nociceptive system and exacerbate pain instead (7,8). The phenomenon has been described in association with prolonged opioid use (8), but also with high doses of short-acting opioids (7). The main mechanism involved in opioid-related pain sensitization include synaptic adaptations within the descending analgesic system and the activation of inflammation-related pain mediators at the neuroimmune interface (8). Based on the combination of μ-opioid receptor affinity and noradrenaline reuptake inhibitory action on the descending analgesic system (26), tapentadol was thus proposed as a potential candidate to treat pain-sensitized patients (4-6,27). However, the results from our empirical testing suggest that repeated tapentadol doses in sensitized knee OA patients may also paradoxically exacerbate pain and the evoked brain response.

In the context of study limitations, it is important to note that the results cannot currently be generalized to other clinical situations, such as pain of neuropathic origin, non-sensitized OA patients, other osteoarthritis pain locations, or different drug dosages. For instance, the duration of treatment in our study was 14 days and the maximum dose achieved was 250 mg a day, whereas, in a recent study by van de Donk et al. (28), higher doses of tapentadol for three months significantly reduced spontaneous pain and temporal summation in a subgroup of chronic low back pain patients with defective central pain inhibition.

Although the present study was based on a number of fMRI assessments deemed adequate to answer the research question, the sample size was limited, for instance, in terms of distinguishing the effects of sex on pain sensitization. This is a relevant issue as there are data indicating that opioid-related pain sensitization may be more severe in males (7). A higher number of assessed patients may also have made it possible to evaluate lateralized brain changes depending on the knee, right or left, stimulated with no need to flip the images for the analysis.

In conclusion, the current clinical trial was unable to demonstrate attenuated brain response to knee painful stimulation in sensitized knee OA patients treated with tapentadol. Instead, the tapentadol effect was paradoxically associated with both spreading the sensory component of the cortical response and stronger activation of prefrontal cortex areas with a recognized role in the appraisal of the pain sensation. Further studies are warranted to explore how OA patients may benefit from powerful analgesic drugs without the associated risks of prolonged use.

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Potential Conflicts of Interest: The authors report no financial interests or potential conflicts of interest.

Data availability statement: The data is available upon request to interested qualified researchers. Data requests should be sent to the Corresponding Author, who can be contacted via 21404jpn@comb.cat.

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Figures

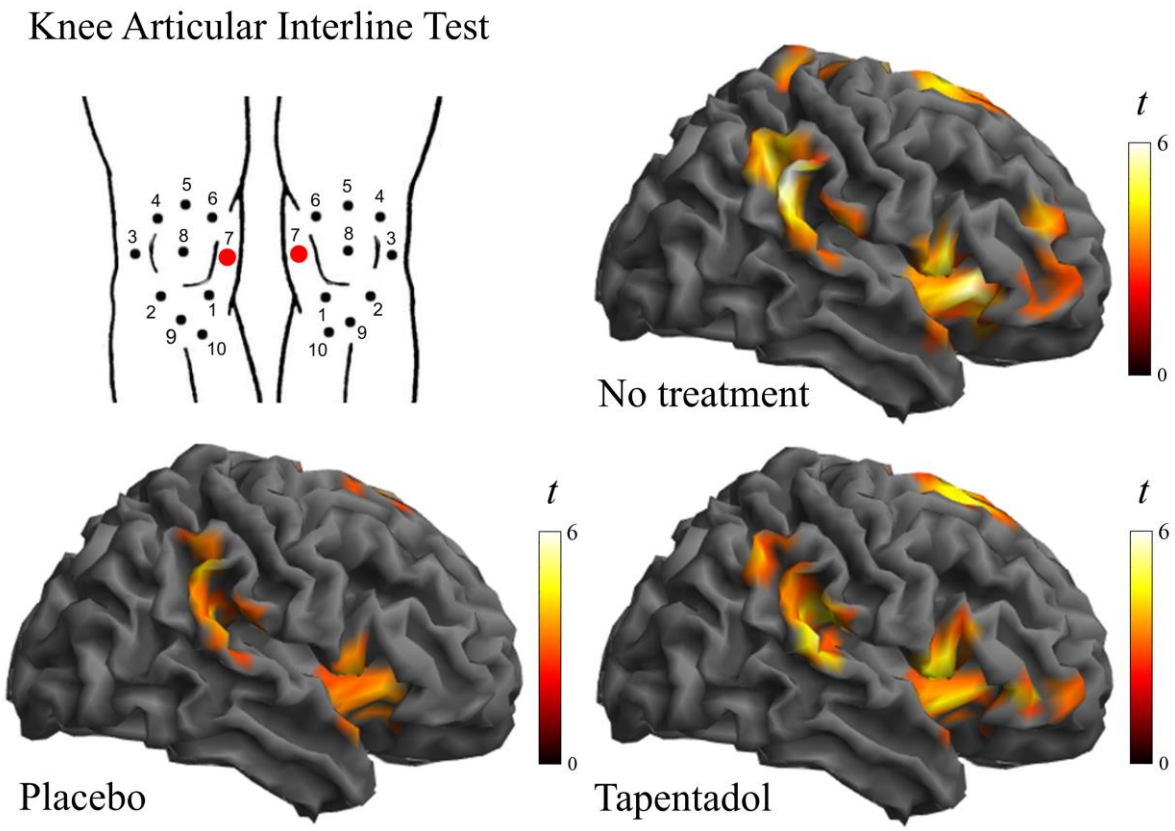

Figure 1. 3D views showing one-sample t-test results from the knee articular interline test analysis.

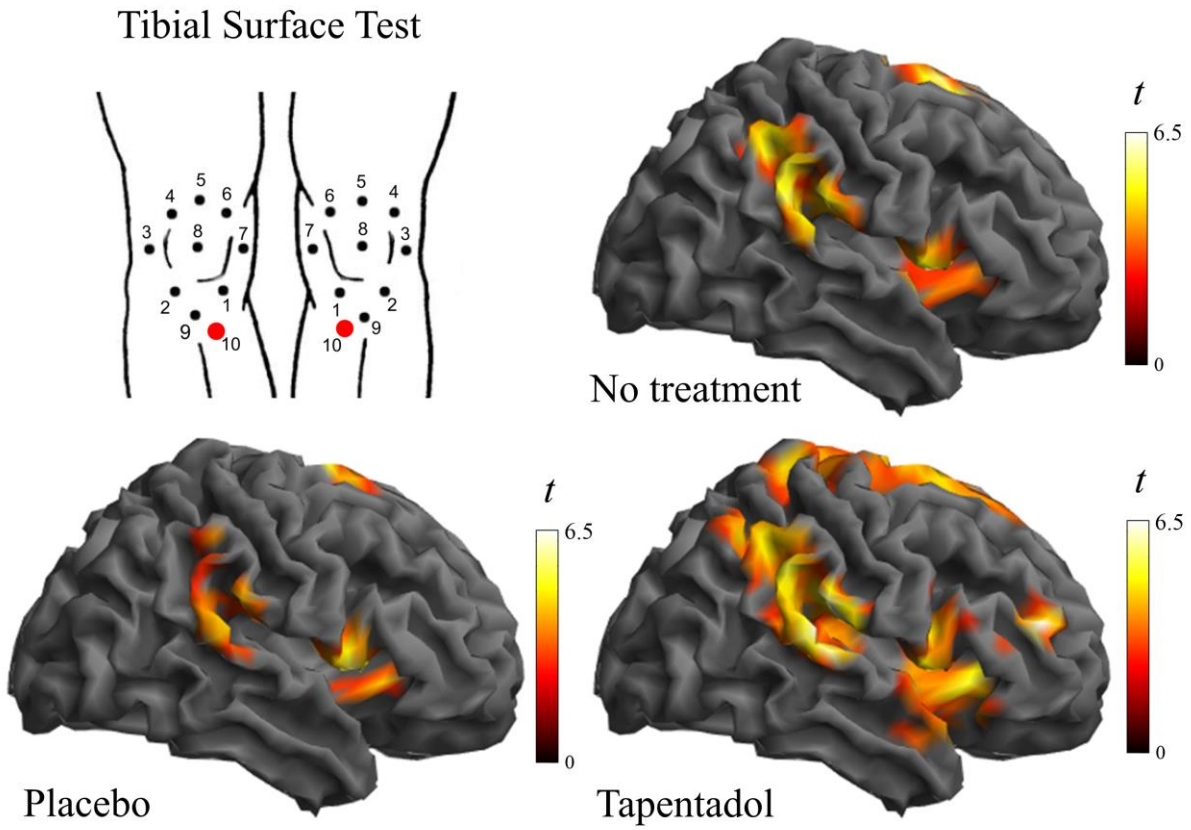

Figure 2. 3D views showing one-sample t-test results from the tibial surface test analysis.

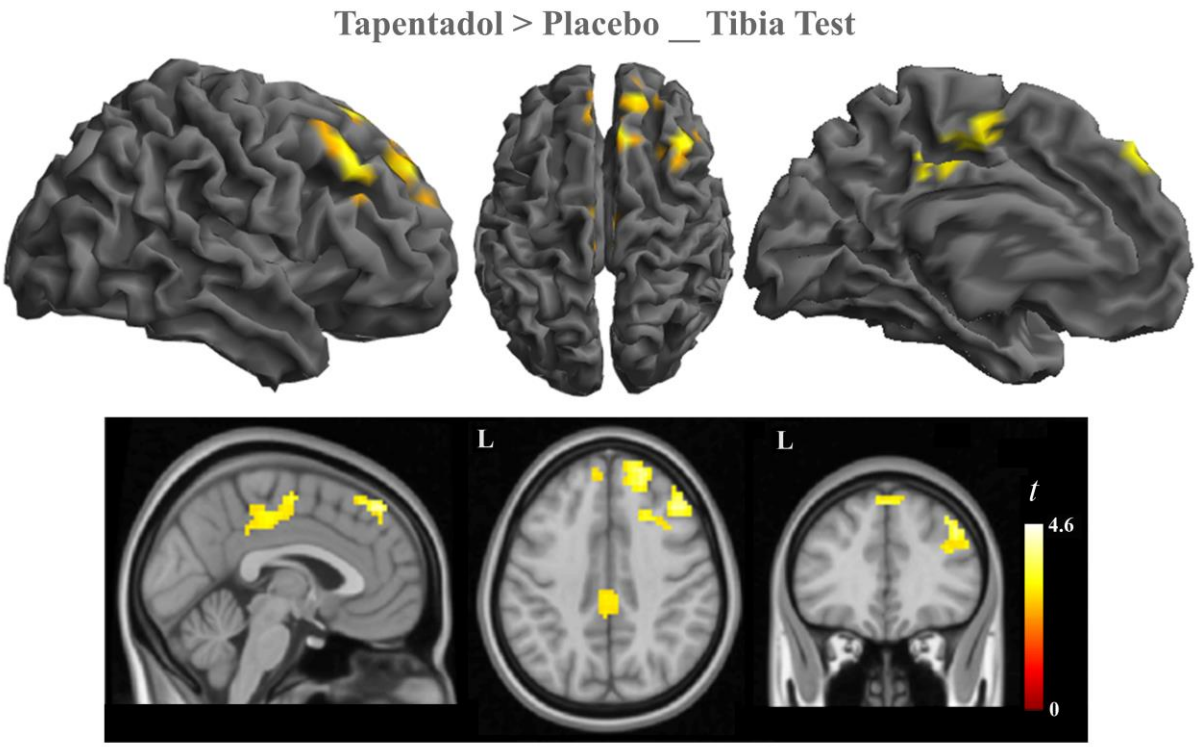

Figure 3. Areas showing stronger activation under tapentadol compared with placebo during tibial surface stimulation.

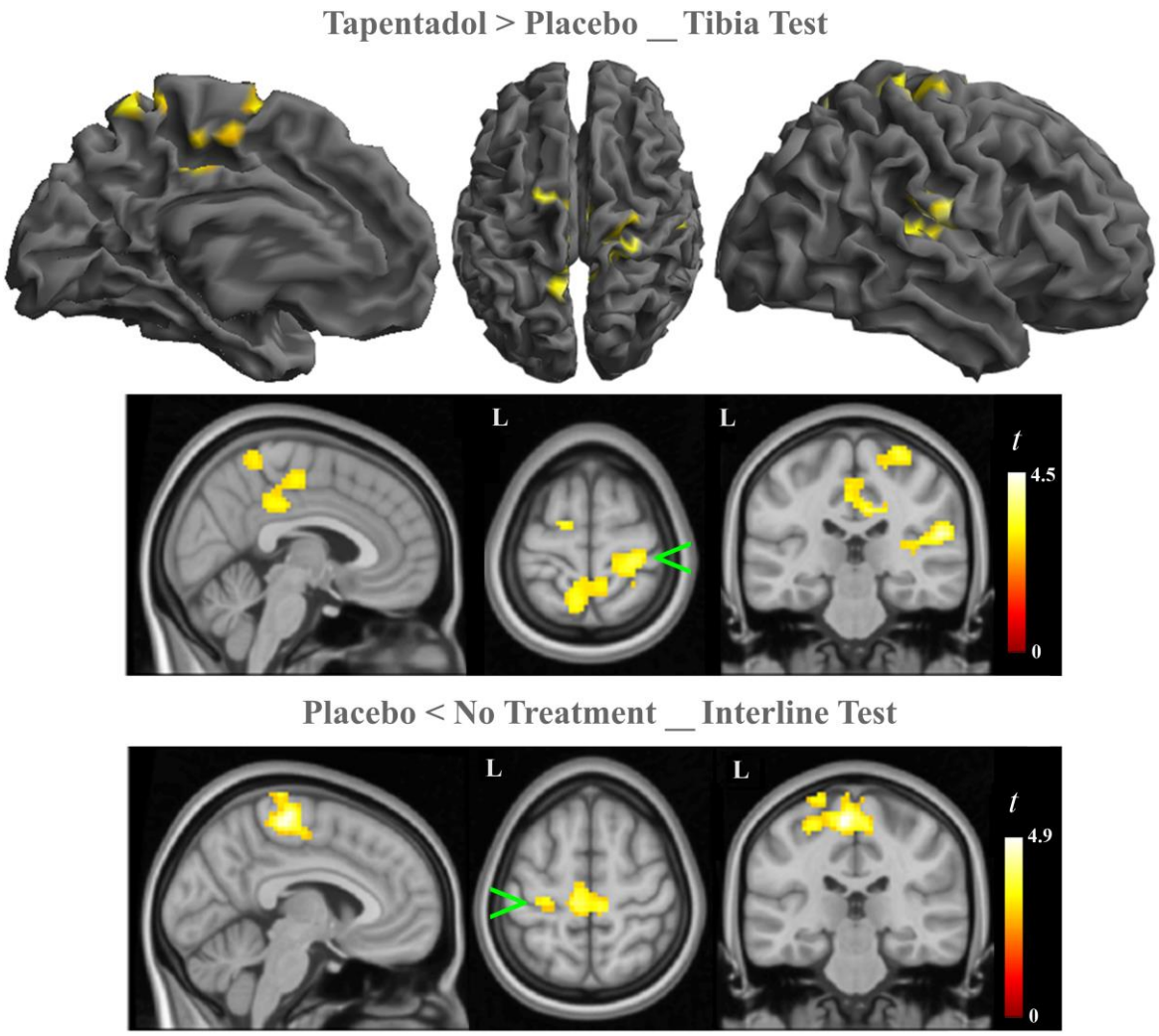

Figure 4. Effects on brain activation identified in the analysis of flipped images. Top views show areas with stronger activation under tapentadol compared with placebo during tibial surface stimulation. The arrowhead indicates the somatosensory cortex ipsilateral to the stimulated knee. Bottom views show areas with activation reduction under placebo compared with no treatment in the articular interline test. The arrowhead indicates the somatosensory cortex contralateral to the stimulated knee.

Table 1. Clinical characteristics of the study sample (n=30)

Age, years	63.4 (± 9.1)
Sex, number F/M	23/7
Radiological severity	2.3 (± 0.5)
WOMAC Index, total	40.4 (± 20.1)
PainDetect	10.4 (± 6.0)
Tibial region pain (regional sensitization)*#	5.8 (± 2.3)
Spontaneous body pain (global sensitization)#	0.4 (± 1.4)
HADS Anxiety score (max. 21 points)	7.1 (± 6.1)
HADS Depression score (max. 21 points)	5.8 (± 4.9)
Tapentadol number of tablets	34 (± 9.1)
Placebo number of tablets	35 (± 7.2)

Data are expressed as mean (± SD). WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. *Pain generated with a pressure of 4 kg/cm^2 during 2 sec. #Rated using an 11-point numerical rating scale. HADS, Hospital Anxiety and Depression Scale.

Table 2. Pain sensitization measures

	Tapentadol n= 30 Mean ± SD	Placebo n= 30 Mean ± SD	No Treat. n= 29 Mean ± SD	Tapentadol vs Placebo df= 29	Tapentadol vs No Treat. df= 28	Placebo vs No Treat. df= 28
Pain Sensitization Global Score	16.5 ± 6.1	14.0 ± 6.4	17.5 ± 5.0	t= 3.0 p= 0.006	t= -1.1 p= 0.278	t= -4.5 p= 0.0001
Clinical Pain Intensity (BPI)	17.8 ± 7.0	15.4 ± 7.6	19.0 ± 6.9	t= 1.6 p= 0.128	t= -0.7 p= 0.521	t= -2.3 p= 0.026
Clinical Pain Spreading	1.4 ± 0.9	1.0 ± 0.7	1.3 ± 0.8	t= 2.8 p= 0.008	t= 0.5 p= 0.636	t= -2.3 p= 0.027
Number of Tender Points	5.8 ± 2.7	5.3 ± 2.5	6.7 ± 2.4	t= 1.3 p= 0.196	t= -2.5 p= 0.018	t= -3.6 p= 0.001
Pain Temporal Summation	1.7 ± 1.7	1.4 ± 2.0	1.7 ± 2.1	t= 0.7 p= 0.474	t= 0.1 p= 0.960	t= -0.8 p= 0.426

BPI, Brief Pain Inventory, items 3 to 6, maximum score 40. No Treat., no-treatment condition.

Supplementary Material

Tapentadol effects on brain response to pain in sensitized patients with knee osteoarthritis

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- **Supplementary Methods**
- **Supplementary Figures**
- **Supplementary Tables**

Supplementary Methods

Functional MRI testing stimuli

Test 1. Pressure stimulation on the articular interline of the knee

The test involved pressure stimulation on the medial articular interline of the selected knee at the tenderest point in each subject. The pressure was exerted with the knee in a 60-degree flexion position using the mentioned algometer. We used identical stimulus intensity for all individuals with 2.5kg/cm^2, 0.5Hz pulses, during each 10s blocks (five pressure pulses per block with pulse duration of 1s and stimulus interval of 1s). The fMRI task included 11 pain blocks of 10s delivered in 6 minutes (Supplementary Figure 2). The intensity of 2.5kg/cm^2 was selected as it consistently provoked moderate pain (5-7 points in an 11-point NRS) in knee OA patients in previous studies (1,2). Each patient was asked to rate subjective pain perceived throughout the fMRI sequence immediately after the acquisition using the 11-point NRS scale. In addition, separate ratings were obtained for pain perceived during the first and last stimulation blocks.

Test 2. Pressure stimulation on the anterior surface of the tibial region

The test similarly involved intermittent, 0.5Hz, pressure stimulation on the anterior (medial) tibial surface at 5cm below the knee interline, in the position of 60-degree flexion and using the study's algometer. Stimulus intensity was 4kg/cm^2 for all subjects. Pressure was applied in 11 blocks of 10s including 5 pressure pulses per block. The intensity of 4kg/cm^2 was selected as the conventional stimulus intensity used to assess primary sensitization disorders (3), generating pain only in tender areas. As in the knee interline test, global, initial and final pain ratings were obtained.

Functional MRI acquisition

A Philips Achieva 3.0 Tesla magnet (Philips Healthcare, Best, The Netherlands), equipped with an eight-channel phased-array head coil and single-shot echoplanar imaging (EPI) software, was used. Functional sequences consisted of gradient recalled acquisition in the steady state (time of repetition [TR], 2000ms; time of echo [TE], 35ms; pulse angle, 70º) within a field of view of 23cm, with a 64 x 64-pixel matrix, a slice thickness of 3.59mm (inter-slice gap, 0mm) and acquisition voxel size of 3.59x3.59x3.59mm. A total of 34 interleaved slices were acquired to cover the whole-brain.

The functional time series consisted of 180 consecutive image sets obtained over 6 minutes. The study included 2 fMRI sequences; Knee Articular Interline test and Tibial Surface test, with identical block paradigm alternating 11 baseline periods of 20 seconds (plus a final baseline period of 30 seconds) and 11 painful stimulation periods of 10 seconds (total six minutes) (Supplementary Figure 2).

Functional MRI preprocessing

Imaging data were processed using MATLAB version 2016a (The MathWorks Inc, Natick, Mass) and Statistical Parametric Mapping software (SPM12; The Wellcome Department of Imaging Neuroscience, London). Preprocessing involved motion correction, spatial normalization and smoothing by means of a Gaussian filter (full-width half-maximum, 8mm). Data were normalized to the standard SPM-EPI template and resliced to 3mm isotropic resolution in Montreal Neurological Institute (MNI) space. Acquisition failures during the tibial test occurred in 1 case in the placebo condition, and in 1 case in the “no-treatment” condition. Therefore, 30 tapentadol-placebo pairs were finally validated for the interline test analysis and 29 pairs for the tibial test analysis.

Control of potential head motion effects. Our primary strategy was based on the acquisition of a large image set allowing us to remove image volumes affected by motion while retaining sufficient signal for a proper analysis. According to fMRI standards and our previous experience, the acquisition of 5 blocks provides a sufficient signal for a block design analysis in activation tasks using powerful stimuli (1,4,5). We acquired a total of 11 blocks in each 6-minute fMRI sequence with the aim of obtaining a minimum of 5 blocks for the analysis after removal. Within-subject, censoring-based MRI signal artifact removal (scrubbing) (6) was used to discard motion-affected volumes. For each participant, mean inter-frame motion measurements (7) served as an index of data quality to flag volumes of suspect quality across the run. At points with mean inter-frame motion > 0.3mm, we discarded the corresponding volume and the succeeding volume. Using this procedure, a mean (±SD) of 3.1 (±9.2) image volumes for the tapentadol, 3.9 (±7.9) for the placebo and 3.7 (±8.0) for the no-treatment condition were removed as to the interline test analysis. In the tibial test, removal was 10.1 (±19.4) volumes for tapentadol, 9.8 (±17.0) for placebo and 5.9 (±8.0) for the no-treatment condition. In no case, did paired t-tests between conditions show significant differences (p values ranging from 0.430 to 0.920). In addition, time series were aligned to the first image volume, six motion-related nuisance regressors and their 6 derivatives were included in the first-level (single-subject) analysis, and individual mean inter-frame motion measures were included as a nuisance regressor in the second-level (group) analyses.

Supplementary References

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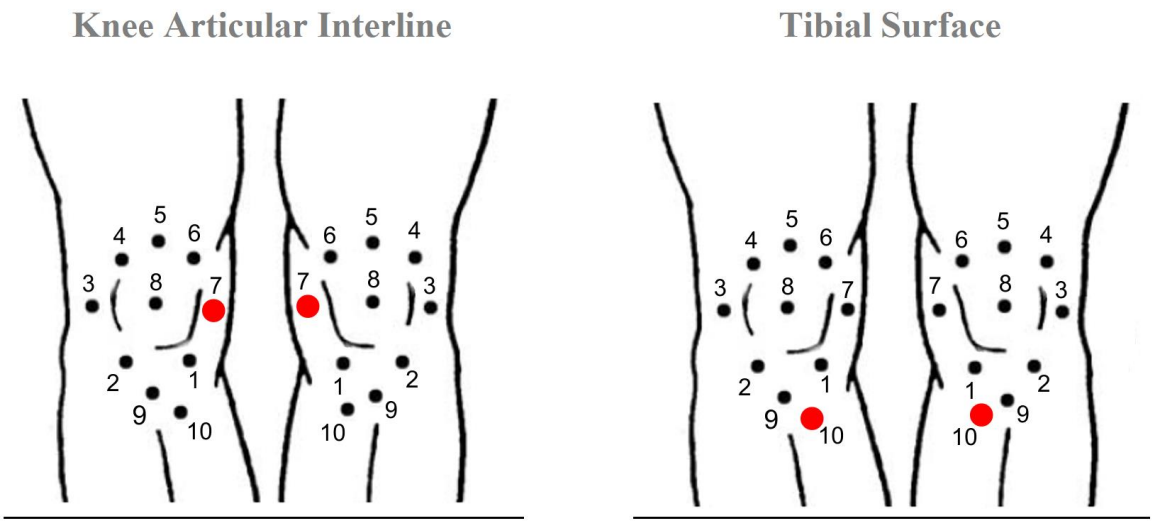
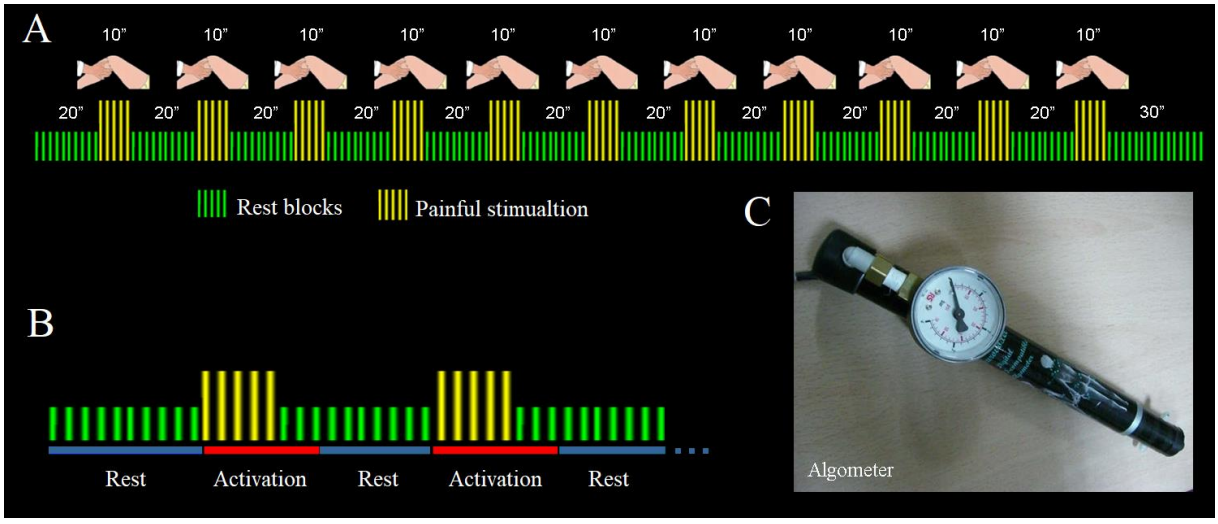
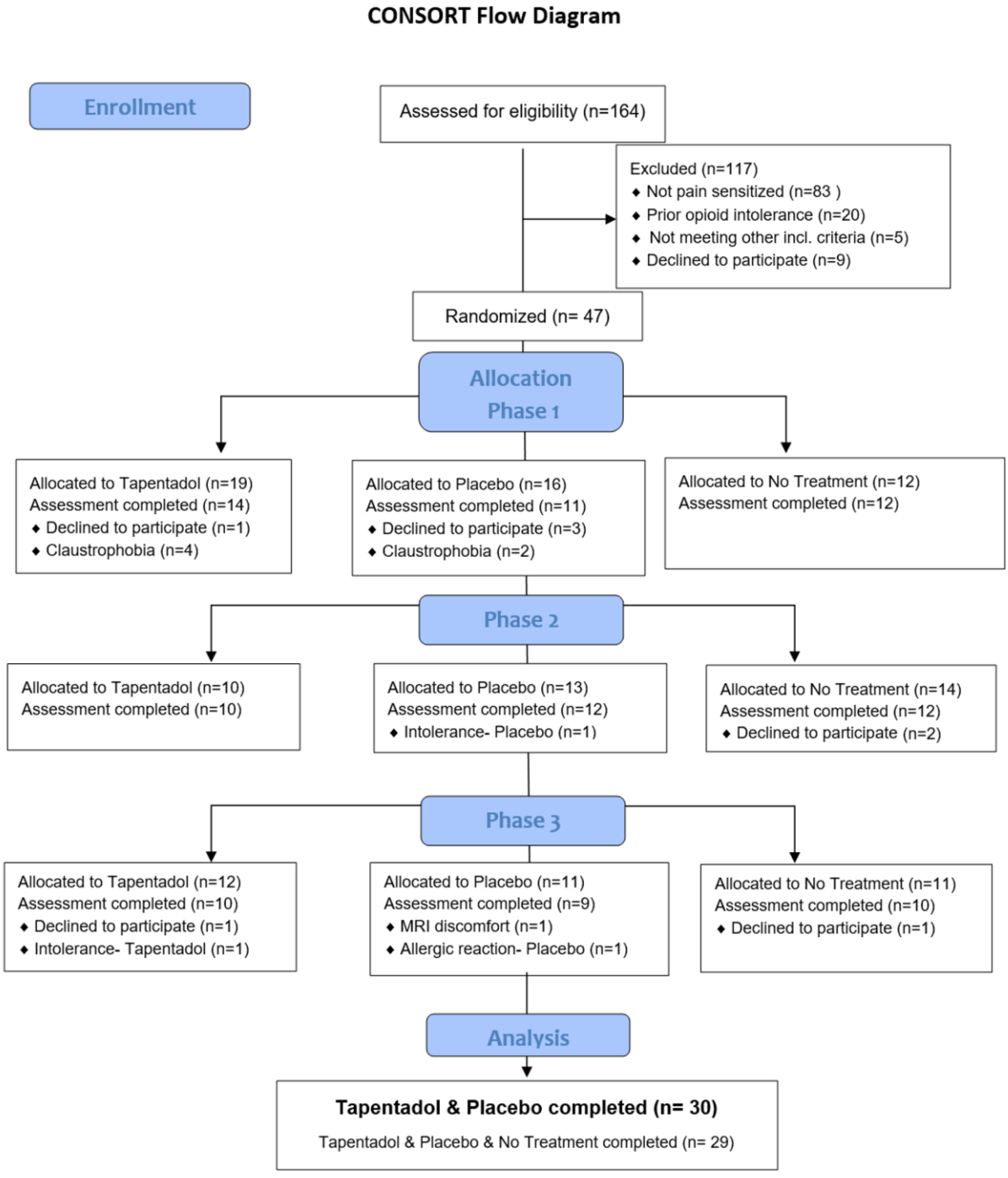
Supplementary Figures



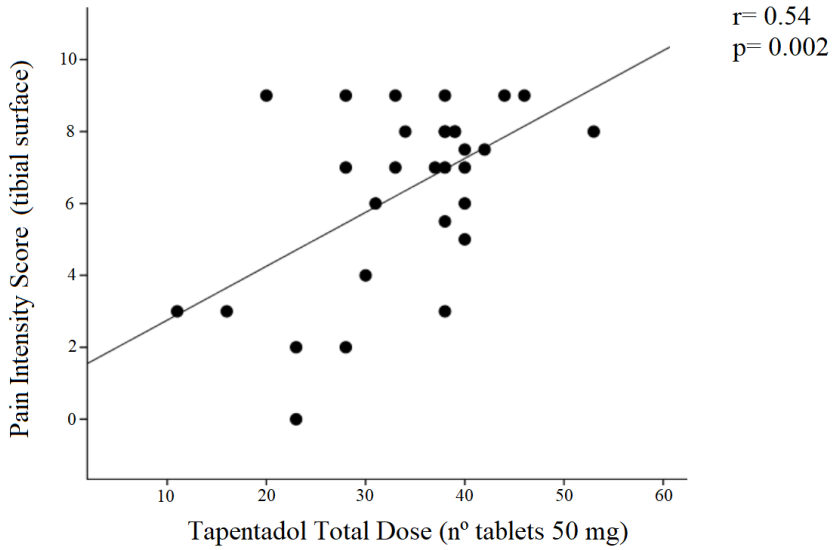
Supplementary Figure 1. Extended version of the Arendt-Nielsen peripatellar map. This map has ten sites located in relation to bone landmark from Arendt-Nielsen 2010 (doi: 10.1016/j.pain.2010.04.003) (sites 1 to 8) and Imamura 2008 (DOI: 10.1002/art.24120) (sites 9 and 10): Site 1: 2 cm distal to the inferior medial edge of patella; site 2: 2 cm distal to the inferior lateral edge of patella; site 3: lateral articular interline; site 4: 2 cm proximal to the superior lateral edge of patella; site 5: 2 cm proximal to the superior edge of patella; site 6: 2 cm proximal to the superior medial edge of patella; site 7: medial articular interline; site 8: at center of patella; site 9: tibial tuberosity/patellar tendon insertion; and site 10: anterior/medial tibial surface, 5 cm distal to the knee interline.



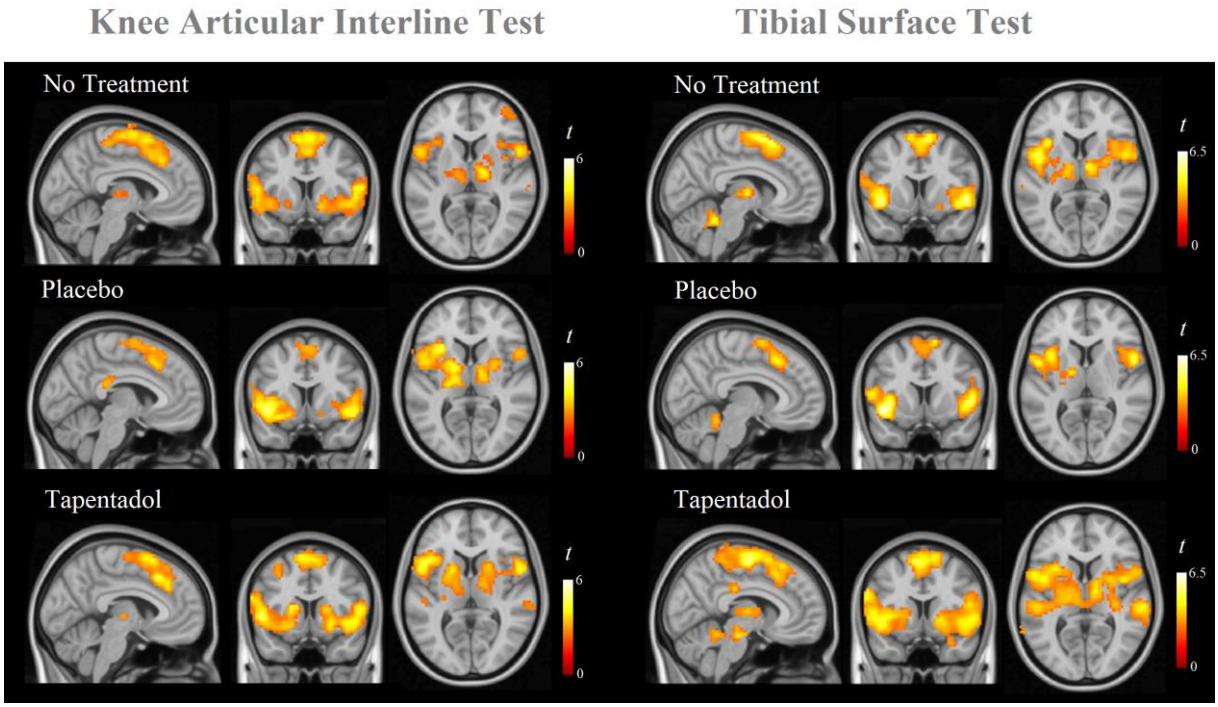
Supplementary Figure 2. A: Block design for the fMRI pressure tests (11 painful blocks plus 12 resting blocks), 360 seconds, 180 volumes. B: Illustration of the task paradigm used for the analysis. A boxcar regressor was generated with the duration of activation blocks adjusted to the actual brain response to our pressure stimulation (i.e., 16s). A delay of 4s was additionally applied to fit with fMRI signal hemodynamics. C: MRI-compatible algometer to apply the pressure stimulus at the selected sites.



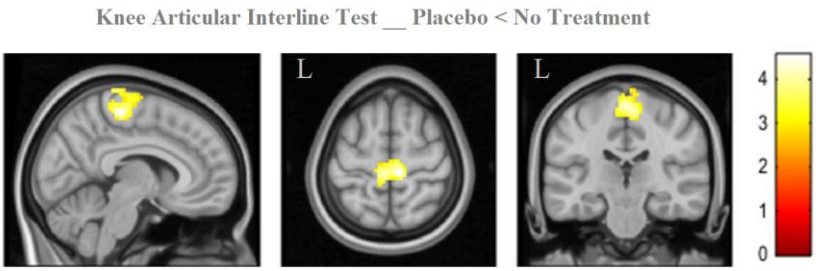
Supplementary Figure 3. Participant flow diagram.



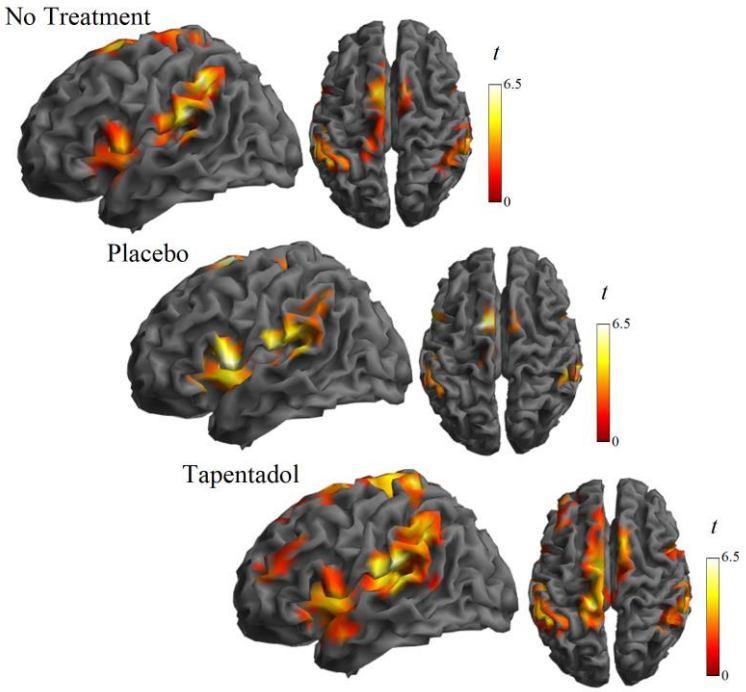
Supplementary Figure 4. Correlation between the number of tapentadol tablets taken during the whole treatment period and 11-point ratings of pain generated by applying pressure on the tibial surface during fMRI testing.



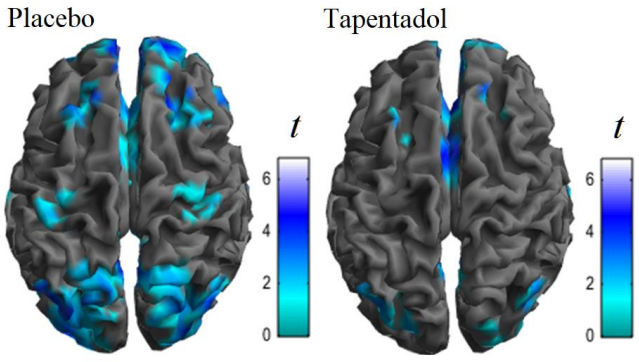
Supplementary Figure 5. Representative orthogonal views showing one-sample t-test results for the three study conditions.



Supplementary Figure 6. The paracentral lobule region showing attenuated response to pressure stimulation on the knee articular interline under placebo compared with the "no treatment" condition.



Supplementary Figure 7. 3D views showing one-sample t-test results from the tibial surface test analysis for the three study conditions. Sub-analysis using flipped images.



Supplementary Figure 8. One-sample results of the contrast activation condition (pressure on) < resting condition (pressure off) at a low threshold ($p < 0.05$), which identifies neural areas inhibited during painful stimulation in the tibial test. Sub-analysis using flipped images.

Supplementary Tables

Supplementary Table 1. Dose Titration Schedule

Step 1	Evening dose of 50 mg (0 / 0 / 50 mg)	3 days
Step 2	100 mg/day (50 /0 / 50 mg)	3 days
Step 3	150-200 mg/day (50-100 / 0 / 100 mg)	3 days
Step 4	250 mg/day (100 / 0 / 150 mg)	To the end

Supplementary Table 2. Pain evoked during fMRI acquisition

	Tapentadol n= 30 Mean ± SD	Placebo n= 30 Mean ± SD	No Treat. n= 29 Mean ± SD	Tapentadol vs Placebo df= 29	Tapentadol vs No Treat. df= 28	Placebo vs No Treat. df= 28
Interline Pain Intensity	5.1 ± 2.9	5.5 ± 2.5	5.8 ± 2.4	t= -0.9 p= 0.384	t= -1.5 p= 0.147	t= -0.7 p= 0.465
Interline T. Summation	1.4 ± 1.7	1.3 ± 2.0	1.1 ± 2.4	t= 0.3 p= 0.795	t= 0.6 p= 0.525	t= 0.5 p= 0.635
Tibia Pain Intensity	6.4 ± 2.5	6.5 ± 2.6	6.7 ± 2.3	t= -0.2 p= 0.826	t= -0.8 p= 0.436	t= -0.6 p= 0.572
Tibia T. Summation	1.6 ± 1.9	1.2 ± 1.8	1.3 ± 2.5	t= 1.5 p= 0.138	t= 0.8 p= 0.450	t= -0.3 p= 0.735

T. Summation, temporal summation. No Treat, no treatment condition. df, degree of freedom.

Supplementary Table 3. Correlation between pain scores and Tapentadol total dose (nº tablets)

	N= 30		N= 27	
	r	p	r	p
Pain Sensitization Global Score	0.14	0.447	0.41	0.036
Clinical Pain Intensity (BPI)	0.21	0.256	0.51	0.007
Clinical Pain Spreading	0.06	0.750	0.43	0.025
Number of Tender Points	0.01	0.974	0.17	0.391
Pain Temporal Summation	0.18	0.347	-0.08	0.704
Interline Pain Intensity (during fMRI)	0.13	0.492	0.42	0.030
Tibial Pain Intensity (during fMRI)	0.54	0.002	0.58	0.002

Analyses including the whole sample (N= 30), and after excluding 3 patients who took 20 tablets or less (N= 27). BPI, Brief Pain Inventory, items 3 to 6.

Supplementary Table 4. Functional MRI statistical results.

	Set-level	*Cluster-level*		*Peak-level*		
	p	***Voxels***	$P_{FWE\text{-}corr}$	***x y z***	***t***	***p***
Articular Interline Test						
Placebo < No Treatment						
Paracentral Lobule		303	0.00008	7 -27 60	4.6	0.00005
Tibial Surface Test						
Tapentadol > Placebo						
Right Prefrontal Cortex _ Medial	0.0001	252	0.001	-5 39 51	4.6	0.00004
Right Prefrontal Cortex _ Lateral		151	0.02	43 27 42	4.1	0.0002
Paracentral Lobule		180	0.009	-5 -12 57	3.4	0.0009
FLIPPED IMAGE						
SUB-ANALYSIS						
Articular Interline Test						
Placebo < No Treatment						
Paracentral Lobule _ Left SI		344	0.00003	-8 -27 60	5.0	0.00002
Tibial Surface Test						
Tapentadol > Placebo						
Paracentral Lobule	0.00002	251	0.003	-2 -30 42	3.2	0.001
Right SI		123	0.094	28 -27 69	3.5	0.0005
Right SII		173	0.02	55 -27 18	4.1	0.00007
Superior Parietal Cortex		121	0.099	-8 -57 66	3.3	0.001

$P_{FWE\text{-}corr}$, P (Family-Wise Error-corrected). x y z, coordinates in Montreal Neurological Institute space. SI, primary somatosensory cortex. SII, second somatosensory cortex at parietal operculum.