Online supplement to: Naproxen Effects on Brain Response to Painful Pressure Stimulation in Patients with Knee Osteoarthritis: A Double-blind, Randomized, Placebo-controlled, Single-dose Study. doi:10.3899/jrheum.131367

Supplementary Material Summary

Supplementary text for Patients and Methods section.

Study protocol. Eligibility criteria.

Sample size rationale

fMRI non-painful sensorimotor task

fMRI acquisition parameters

fMRI pre-processing

Supplementary Figure 1.

Supplementary Figure 2.

Supplementary Figure 3.

Supplementary Figure 4.

Supplementary Figure 5.

Supplementary Figure 6.

doi:10.3899/jrheum.131367

Supplementary text for Patients and Methods section

Study protocol. Eligibility criteria

A subject was eligible for inclusion if all of the following criteria applied: (i) a diagnosis of OA and suitable for the study as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, and cardiac monitoring; (ii) to have a radiological and clinical diagnosis of OA based upon the American College of Rheumatology (ACR) criteria (1) affecting at least one knee for a minimum of 3 months in symptom duration prior to screening. The symptoms should be significantly worse in one knee if both knees were affected; (iii) male or female ≥ 45 years of age; (iv) a minimum and a maximum of 4 and 8 out of 10 on the numerical rating scales (NRS) at screening referring "pain at present" and/or a requirement for the use of an analgesic for the pain in the OA knee for most days during the previous 3 months. In addition, baseline pain must be stable for at least 72 hours prior to session 1; (v) a non-childbearing potential females; (vi) body weight <120 kg and Body Mass Index (BMI) within the range 15 – 35 kg/m^2.

Exclusion criteria were: (i) to have a positive pre-study drug/alcohol screen or history of alcohol abuse within 6 months of the study; (ii) use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days or 5 half-lives prior to the first dose of study medication; (iii) history or presence of gastro-intestinal, hepatic or renal disease or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs; (iv) subject was taken any drug known to induce or inhibit hepatic drug metabolism in the 15 days prior to the screening visit at the start of the study; (v) subjects who have asthma or a history of asthma, (vii) subjects

smoking more than 20 cigarettes per day; (viii) secondary causes of arthritis of the knee; (ix) had lower extremity surgery within 6 months prior to screening or scheduled for surgery of any kind during the study period in the affected knee; (x) significant prior injury to the index knee within 12 months prior to screening; (xi) disease of the spine or other lower extremity joints to affect the index knee or any other musculoskeletal or arthritic condition that may affect the interpretation of clinical efficacy and/or safety data; (xii) use of any analgesic, cyclooxygenase-2 (COX-2) inhibitor or nonsteroidal anti-inflammatory drugs (NSAIDs), other than study defined rescue therapy within 5× half-life prior to the first dosing day or during the study; (xiii) corticosteroid use prior to baseline; (xiv) received hyaluronan injections into index knee within the previous six months prior to baseline; (xv) initiation of or change to an established physiotherapy program within 2 weeks prior to baseline or during the study period.

Sample size rationale

There is not a consensus as to sample size estimation for fMRI studies, so in the current protocol, we use data from a previous study on the same topic by our research team. In a study of brain response to pressure painful stimulation of an analgesic drug in 19 patients with chronic pain, we found a mean difference in the reduction of fMRI signal in the SII of 0.25 arbitrary units (fMRI beta values) and a standard deviation of the difference of 0.38 units between treatment and no treatment conditions, using paired T-test (non-published data). If the true difference between conditions is 0.25 units we would need to study at least 21 subject pairs to be able to reject the null hypothesis with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. Assuming a 15% of withdrawals by different reasons, at least a minimum of 25 subjects should be studied.

fMRI non-painful sensorimotor task

To discard possible global effects on fMRI signal induced by naproxen (possible vascular reactivity and/or unspecific effects on the brain neuronal activity) a non-pain related sensorimotor task was conducted. The fMRI sequence was based on a block design paradigm, including blocks with across fixation onto the screen and a visual intermittent checkerboard pattern joining a sound (control and experimental conditions, respectively). The task consisted on a 4 min sequence, comprising 8 blocks (4 per condition, starting with a cross fixation block). Each block lasted 30 sec. Briefly, patients were scanned while performing a blocked task that consisted of performing finger opposition movements while watching a 3Hz-flashing checkerboard square and hearing 15 rapid different tones presented 5 times across a block (75 tones per block; 400 ms of duration each). Stimuli for the sensorimotor control task were generated and timing controlled by PresentationTM software (Neurobehavioral Systems Inc., USA, http://www.neurobs.com/) and presented to patients using MRI-compatible high-resolution goggles and headphones (VisuaStim Digital System, Resonance Technology Inc., Northridge, CA).

fMRI acquisition parameters

Functional sequences consisted of gradient recalled acquisition in the steady state (time of repetition [TR], 2000 ms; time of echo [TE], 50 ms; pulse angle, 90º; field of view [FOV], 24 cm; 64 x 64-pixel matrix; slice thickness, 4 mm (inter-slice gap, 1.5 mm)). Twenty-two interleaved slices, parallel to the anterior-posterior commissure line, were acquired to cover the whole-brain. The acquisitions were preceded by 4 additional dummy images allowing the pain MRI signal to reach equilibrium.

fMRI pre-processing

All fMRI data were processed and analyzed using the Statistical Parametric Mapping (SPM5) package, Wellcome Department of Imaging Neuroscience [http://www.fil.ion.ucl.ac.uk/spm/software/spm5/], running in Matlab 7. Images were realigned, normalized to Montreal Neurological Institute (MNI)-space (voxel size = 3*3*3 *mm3*) and smoothed with a full width at half maximum (FWHM) Gaussian kernel of 8 mm.

In this study, and consistent with previous works (2), we have observed, by means of an exploratory temporal independent component analysis (ICA) approach (3,4), that the duration of brain response to a 10-sec painful stimulation approaches to 16 sec. So, our main analysis for the fMRI painful task is based on a 16-sec activation condition for each experimental block. ICA was performed using the Group ICA for fMRI Toolbox (GIFT v1.3d; http://icatb.sourceforge.net) running on Matlab 7 (Supplemental Figures 1 & 2).

References

1. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee. Arthritis Rheum 2000;43:1905–15.

2. Pujol J, López-Sola M, Ortiz H, Vilanova JC, Harrison BJ, Yucel M, et al. Mapping brain response to pain in fibromyalgia patients using temporal analysis of fMRI. PLoS One 2009;4:e5224.

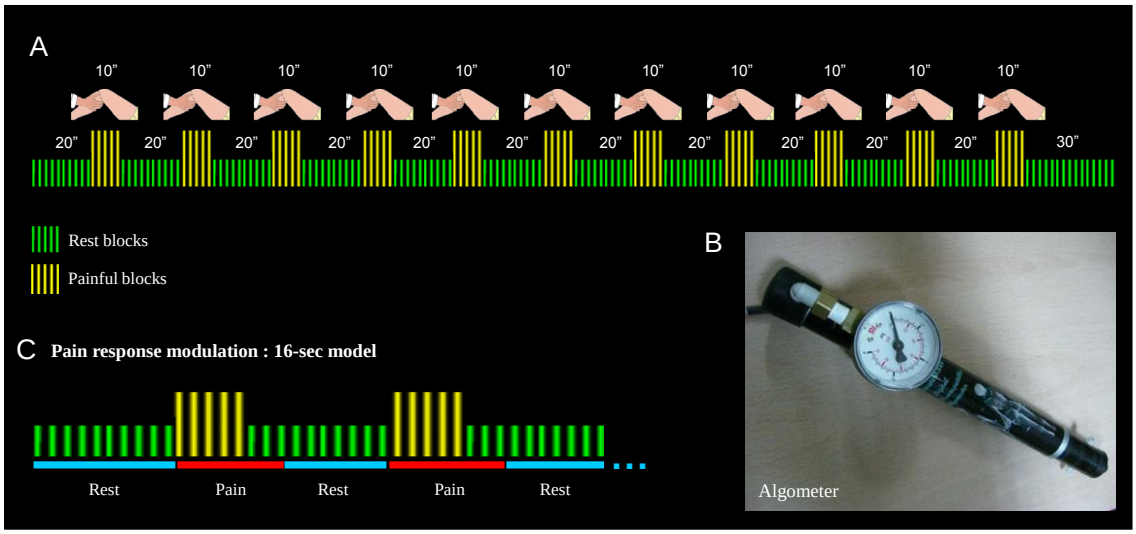
3. Calhoun VD, Adali T, Pearlson GD, Pekar JJ. A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp 2001;4:140-151.

4. Calhoun VD, Adali T, Pekar JJ. A method for comparing group fMRI data using independent component analysis: application to visual, motor and visuomotor tasks. Magn Reson Imaging 2004;22:1181-91.

Online supplement to: Naproxen Effects on Brain Response to Painful Pressure Stimulation in Patients with Knee Osteoarthritis: A Double-blind, Randomized, Placebo-controlled, Single-dose Study.
doi:10.3899/jrheum.131367

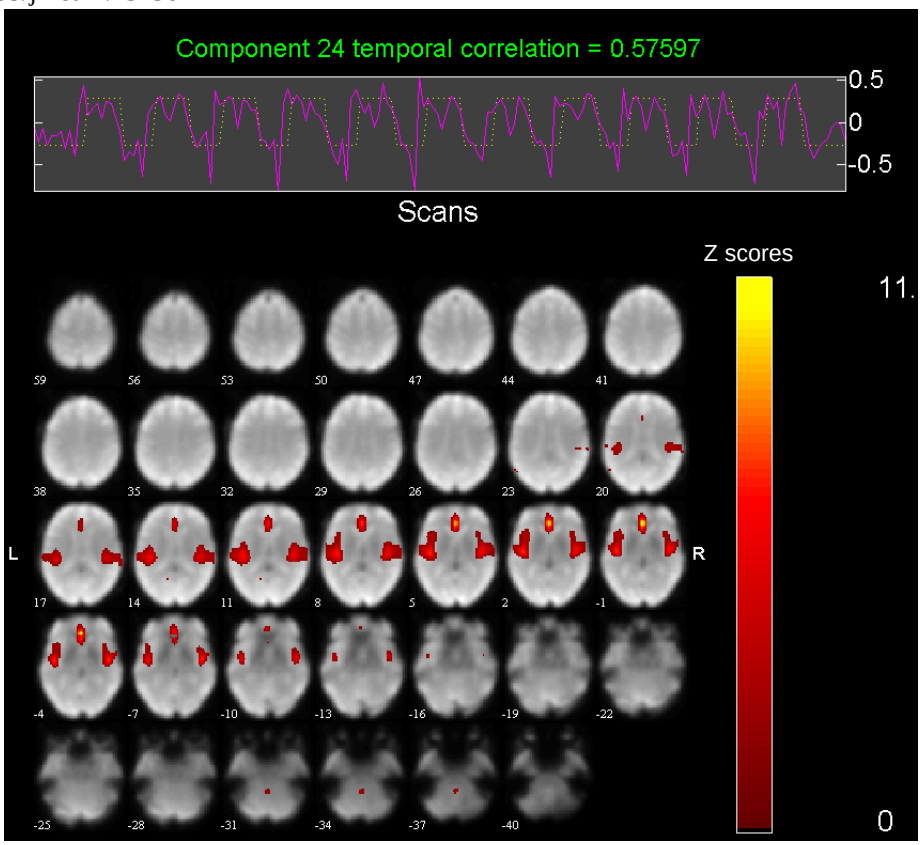
Supplementary Figures

Supplementary Figure 1. Mechanical stimulation of the knee: fMRI painful pressure task. (A) Block design for the pressure task (11 painful blocks plus 11 resting blocks), 360 s, 180 volumes. (B) Home-made algometer to apply the pressure of the tenderest knee point. (C) Yellow: original painful stimulus (10-s duration blocks); green: original resting blocks (20-s duration). Blue & red lines correspond to the new SPM models created in order to estimate and model the data. Blue line: parts of the task modeled into SPM program as resting blocks; Red lines: parts of the task modeled into SPM program as activation blocks (16-s of activation condition).

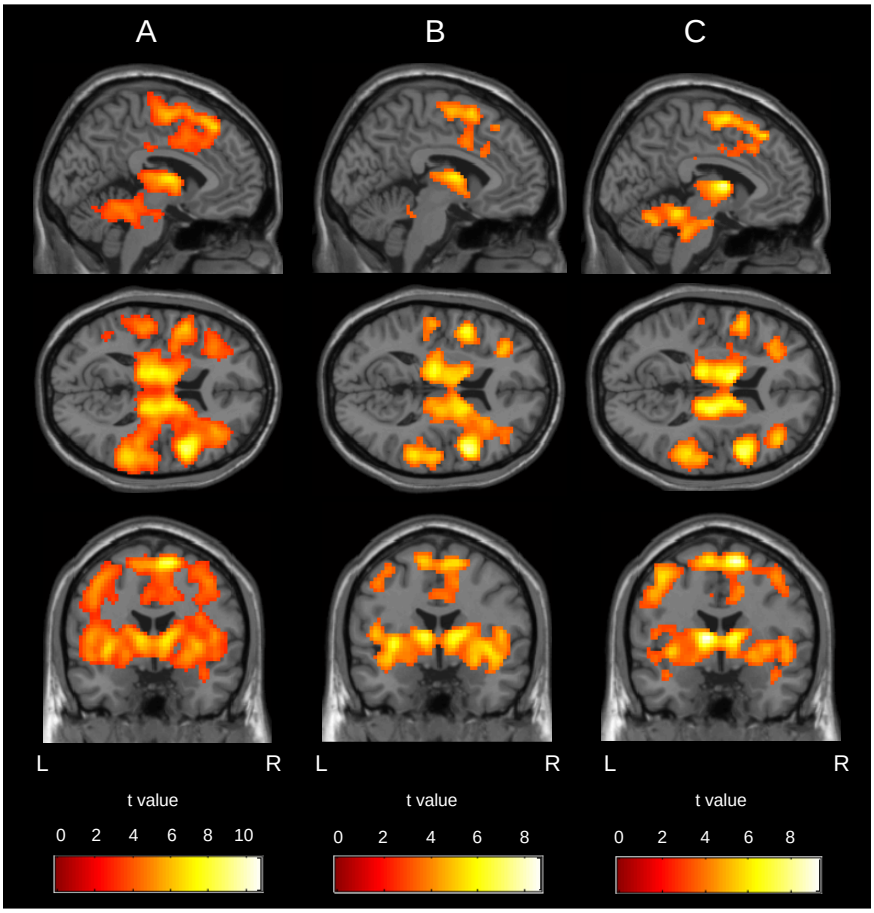


Supplementary Figure 2. A component (brain network) derived from the ICA analysis involving regions relevant in pain response. This component shows brain voxels with a particular activation dynamics, representing actual brain response to the delivered painful stimulation. This temporal time course consists on a robust activation in each stimulation block. Nevertheless, the duration of brain activation differ from the duration of painful stimulation. That is, as a mean, patients showed duration in brain activation 6 sec longer than duration of painful stimulation, total 16 seconds per each activation period. Pink line: mean of the temporal time-course activity of the voxels contained within this component. This component shows those voxels whose temporal behavior (activation) is positively correlated with the temporal time-course described by the pink line. White spot line: example of a theoretical block model (activation blocks versus resting blocks), but considering 16 seconds of painful response -10 seconds of real painful stimulation plus 6 seconds of post stimuli sustained response-. The bar indicates the Z-score values for each voxel forming the specific component.

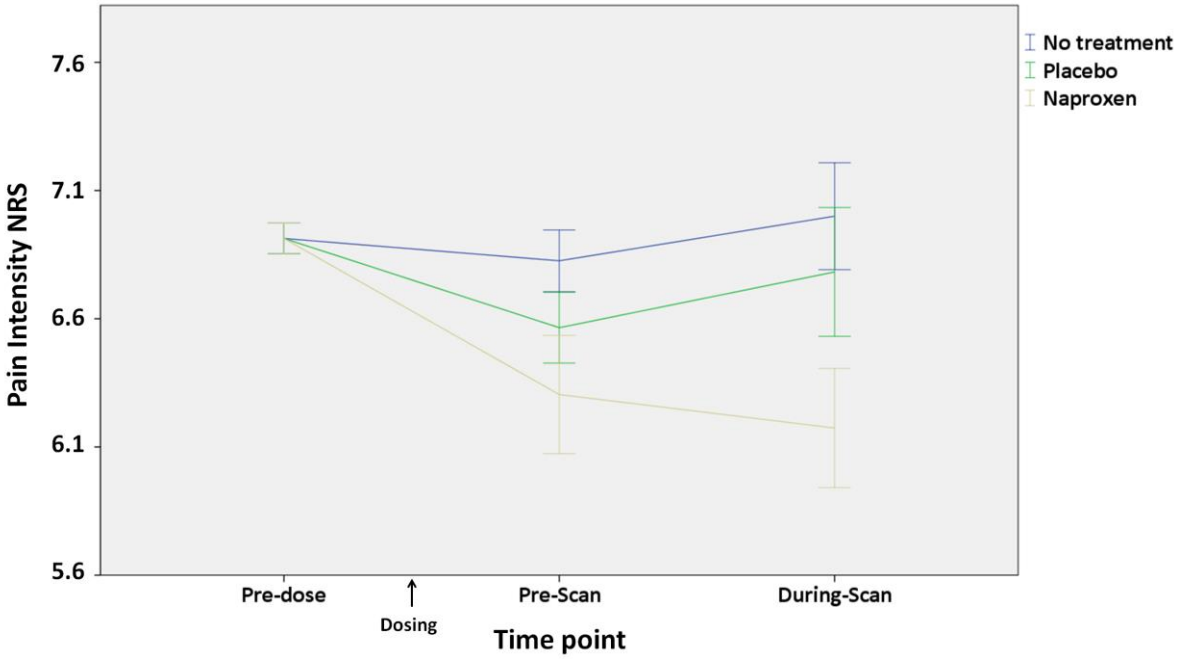
Online supplement to: Naproxen Effects on Brain Response to Painful Pressure Stimulation in Patients with Knee Osteoarthritis: A Double-blind, Randomized, Placebo-controlled, Single-dose Study. doi:10.3899/jrheum.131367



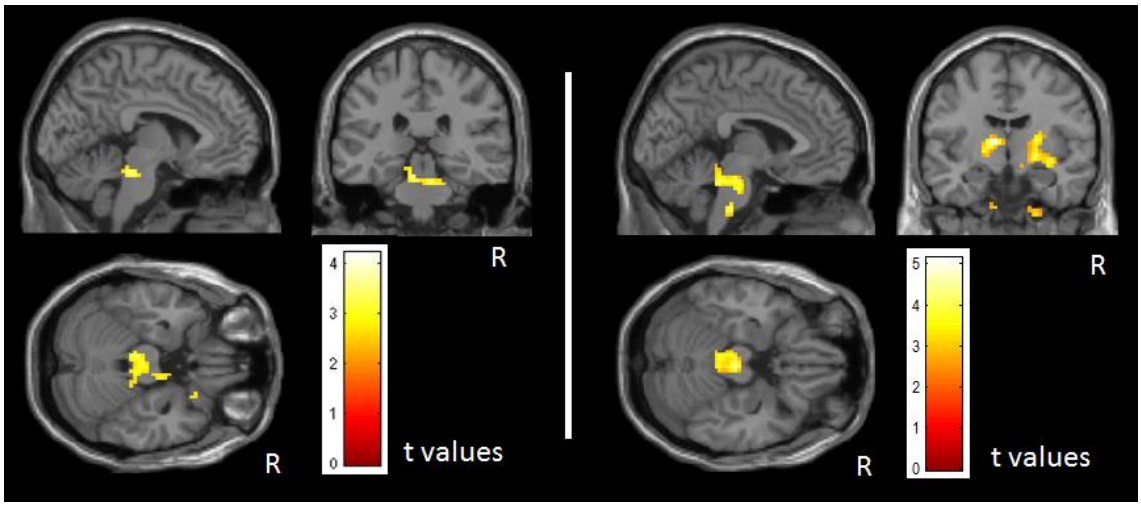
Supplementary Figure 3. Brain activation during the fMRI painful pressure task. (A) No treatment. (B) Placebo. (C) Naproxen. N = 23. Display: t =3, 200v. L: Left; R: Right.



Supplementary Figure 4. Pain Numerical Rating Scale (NRS) scores during the fMRI painful pressure task. Data is shown as line graphs; lines representing treatment conditions at different time points (pre-dose, pre-scan, during-scan; same session). During-scan time point illustrates the pain felt during a whole fMRI painful pressure sequence (6.30 mins). Significant differences were found between no treatment and naproxen for during-scan pain ratings.



Supplementary Figure 5. Clinical (non-evoked) pain correlations. Correlation between subjective scores of ongoing pain (affected knee collected at screening visit) with (i) baseline (no treatment) brain activation (left panels) and (ii) brain activation map of the difference between naproxen and no treatment (right panels). Significant correlations were observed in the brainstem (left panel peak coordinates x,y,z: -5,-30,-24; t= 4.0. Right panel x,y,z: 3,-21,-24; t= 4.5), left basal ganglia/thalamus (right panel x,y,z: -9,-6,9; t= 5.2) and right basal ganglia (right panel x,y,z: 24,-6,0; t= 4.2). Display: t =2.5, 10v. R: Right.



Online supplement to: Naproxen Effects on Brain Response to Painful Pressure Stimulation in Patients with Knee Osteoarthritis: A Double-blind, Randomized, Placebo-controlled, Single-dose Study.
doi:10.3899/jrheum.131367

Supplementary Figure 6. Brain activation during the fMRI sensorimotor task under the no treatment. N = 25. Display: t =3, 200v. L: Left; R: Right.