nociceptors. MSCs were recorded in the cell-attached configuration and were stimulated with a high-speed pressure clamp (HSPC) device.
Results: Our behavioral observations indicate that MIA-injected mice become hypersensitive to knee flexion and extension. Electrophysiology recordings from acutely dissociated knee nociceptors indicate that there are no changes in the resting membrane potential. However, our data indicates that the activation threshold of MSCs in the nociceptors of OA mice is significantly lower than that of nociceptors from naïve mice. Moreover, there is a greater elicited mechanosensitive current in OA nociceptors.
Conclusions: Our data suggest that the lowered threshold of MSCs may contribute to the mechanical hypersensitivity observed in behavioral tests. MSCs in nociceptors may be a novel therapeutic target in the treatment of OA pain.

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LYSOPHOSPHATIDIC ACID CONTRIBUTES TO THE DEVELOPMENT OF NEUROPATHIC PAIN IN RODENT KNEE JOINTS

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Purpose: Since a subset of osteoarthritis (OA) patients are unresponsive to classic analgesics, it has been postulated that OA pain may have a neuropathic component. The lipid mediator lysophosphatidic acid (LPA) is found in arthritic joints and has been shown to cause peripheral neuropathy and neuropathic pain-like symptoms in skin. The present study investigated the effect of LPA on joint nerve morphology and pain generation in rats.
Methods: Male Lewis rats (300-350g) had 50μg of LPA injected into their right knee joint and allowed to recover for 3 weeks. Animals were then euthanized and the ipsilateral saphenous nerve was removed and fixed in 4% paraformaldehyde. The nerve was then prepared and sectioned for electron microscopic analysis of axon myelination using G ratio calculations (internal neuronal area divided by total area). Dorsal root ganglia (DRG L3-L5) were also removed, fixed and embedded in optimal cutting temperature compound. Sections of DRG were stained for the nerve degeneration marker ATF-3. In separate studies, 50μg, 100μg and 200μg of LPA were injected into the right knee and pain assessed 1, 4, 9, 15 and 51 days post intra-articular injection by differential weight bearing using an incapacitance tester.
Results: Intra-articular injection of LPA caused a significant increase in G-ratio ($P<0.05$) indicative of demyelination. Similarly, LPA treatment caused a heightened expression of ATF-3 in ipsilateral nerve cell bodies. In animals assessed for pain, all 3 doses of LPA elicited a dose-dependent pain response. The pain persisted after a single LPA injection out to 51 days post injection.
Conclusions: These data indicate that intra-articular injection of LPA caused a peripheral neuropathy with associated pain behaviour. Pharmacological blockade of LPA receptors or a reduction in its formation may be an efficacious means of controlling neuropathic pain in the subset of OA patients that do not respond to classic analgesics.

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CORTICAL SINGULARITY OF KNEE OSTEOARTHRITIS PATIENTS AND THEIR RESPONSE TO DULOXETINE OR PLACEBO TREATMENT

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Purpose: Structural and functional brain changes have been shown to be associated with the development and regression of chronic pain. This study was undertaken to determine the brain structural characteristics that correlate with response to duloxetine (DLX) and placebo (P) treatment in patients with knee OA.
Methods: 40 participants were entered into a randomized, controlled trial of DLX 60 mg qd vs matching P. All participants met ACR radiographic and clinical criteria for knee OA, had pain ≥ 4 on 11 point NRS scale, met all inclusion and exclusion criteria, and were treated for 4 months with pain measurements at weeks 0, 2, 3, 6 and 16. Anatomic MRI scans were done at baseline and at end of treatment. The total gray matter volume of the brain was obtained using the SIENAX tool from FSL and cortical gray matter density (GMD) changes were evaluated using a voxel based morphometry approach (FSL-VBM). To evaluate structural brain properties, longitudinal contrast was made by using a two-way repeated measure ANOVA design.
Results: Although there was no overall difference in the mean pain response between treatment groups ($p=0.87$), both the DLX and P groups included participants who had a significant pain response (≥ 20% pain decrease from baseline, hence classified as "responders or +") as well as those with lesser or no response ("non-responders or -"). When the brain morphology of each of these 4 groups (DLX + and DLX -; P + and P -) was assessed from their baseline visits, prior to any treatment, significant regional GMD differences were observed in extensive regions across the brain (Fig. 1). Whole-brain voxel-wise VBM contrast (before - after treatment) revealed that DLX-treated patients underwent modification in GMD in the left precentral gyrus, left middle frontal gyrus and bilateral ACC (figure 2A). Interestingly, when patients positively responded to their treatment, independent of the compound received, differences in GMD were observed only in the left precentral gyrus (figure 2B). In addition, regions in the left middle frontopolar (figure 2C) and inferior temporal gyri showed GMD changes when DLX induced pain relief. We thus show that some cortical regions presenting GMD reorganization were shared among all 4 groups studied, suggesting that a proportion of gray matter structural modification may be naturally occurring in time while other regional changes are directly related to treatment received.
Conclusions: Treatment in participants with OA pain is affecting cortical reorganization in a way that is dependent on the type of treatment, the treatment response and the interaction of both. Understanding how placebo and pharmacological treatment affect structural brain properties is important to allow more personalized approaches to therapy in OA pain.

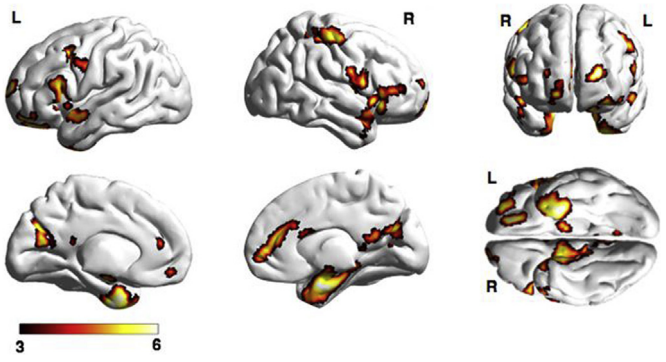

Figure 1. **Differences in Gray matter density (GMD) is observe within the 40 OA subjects before the beginning of the treatment**. This f map was obtained after performing a cross-sectional one-way ANOVA on the 40 OA subjects at the first scanning session. This map revealed the areas where GMD differences are identified when comparing the 4 sub-groups of OA subjects present in our study.

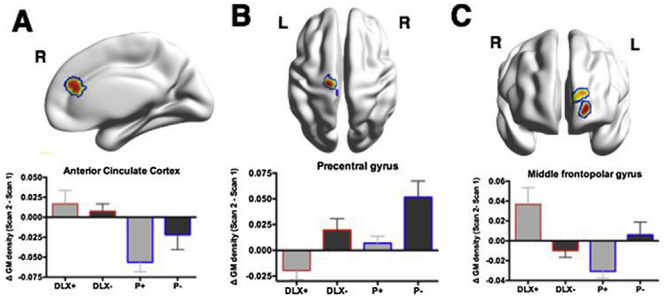

Figure 2. Treatment received, pain decrease and their interaction induce unique gray matter reorganization. Two-way repeated measure ANOVA revealed that **A)** DLX and P induce opposite GM modification in bilateral ACC. B) Response to the treatment is affecting cortical changes in a region in the left precentral gyrus (primary motor cortex) and **C)** Prefrontal cortex undergoes high GM reorganization for DLX-patients that show pain decrease. DLX = Duloxetine. P = Placebo, + = responders, - = non-responders.