

A higher grey matter density in the amygdala and midbrain is associated with persistent pain following total knee arthroplasty

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Running head: Brain structure after knee arthroplasty

Abstract

Objective: The development of persistent pain following total knee arthroplasty (TKA) is common, but its underlying mechanisms are unknown. The goal of the study was to assess brain grey matter structure and its correlation with function of the nociceptive system in people with good and poor outcomes following TKA. **Subjects:** 31 people with LOW_PAIN (<3/10 on the Numerical Ratings Scale (NRS)) at 6 months following TKA and 15 people with HIGH_PAIN ($\geq 3/10$ on the NRS) were recruited into the study. **Methods:** Grey matter in key brain areas related to nociception was analysed using voxel-based morphometry (VBM). Nociceptive facilitatory and inhibitory processes were evaluated using quantitative sensory testing (QST). QST scores and grey matter density in pre-specified brain regions were compared between the LOW_PAIN and HIGH_PAIN groups. Regression analyses were used to analyse the associations between the grey matter and the QST scores. **Results:** There were no between-group differences in QST measures. In the VBM analysis, the HIGH_PAIN group had a higher grey matter density in the right amygdala, right nucleus accumbens, and in the periaqueductal grey (PAG), but lower grey matter density in the dorsal part of the left caudate nucleus. Grey matter density in the right amygdala and PAG correlated positively with temporal summation of pain. **Conclusions:** Persistent pain at 6-months after TKA is associated with a higher grey matter density in the regions involved in central sensitisation and pain-related fear, which may contribute to the development of persistent pain after surgery.

Key words: total knee arthroplasty; persistent postoperative pain; voxel-based morphometry; VBM; quantitative sensory testing; QST

Introduction

Total knee joint arthroplasty (TKA) is the recommended treatment for people with advanced knee osteoarthritis who do not respond to conservative management (1). While most patients experience considerable pain relief following TKA, approximately 15-40% report ongoing pain at 6-months after surgery (2-5).

It is not fully understood why pain may persist after TKA. One of the potential factors contributing to the development of persistent pain in some patients is a different adaptation of the nociceptive system that may occur before or after TKA. Quantitative sensory testing (QST) can be used to assess the function of the nociceptive system, including pain facilitatory and inhibitory processes. Previous studies have reported that patients with osteoarthritis have enhanced facilitation and reduced inhibition of nociceptive input, manifesting on QST as a lower pressure and mechanical pain threshold, greater temporal summation of pain, and impaired descending pain inhibition (6-8). Enhanced nociceptive facilitation and impaired inhibition prior to joint replacement are associated with less pain relief following surgery (9). Some studies have demonstrated that these processes normalise following joint replacement (6, 10), while others (11) have shown that such normalisation occurs only in patients with low pain at 12-months post-surgery and that in patients with higher postsurgical pain nociceptive facilitation persists.

Altered pain processing may be associated with structural brain changes, which reflect the adaptation of the supraspinal components of the nociceptive system. A recent meta-analysis (12) on structural brain changes in chronic pain reported altered grey matter density in key brain regions involved in nociceptive processing, including the insula, basal ganglia, thalamus, periaqueductal grey (PAG), and the primary somatosensory cortex (S1).

Studies that specifically have involved populations with lower limb osteoarthritis also described grey matter changes in similar regions, but additionally in the amygdala, and anterior cingulate cortex (13-16). Importantly, two longitudinal studies in patients undergoing total hip joint replacement reported a reversal of changes in grey matter density in the months following joint replacement (14, 15). However, it is uncertain how such structural adaptations may relate to the extent of pain relief following surgery, or whether they are associated with functional adaptations of the nociceptive system.

The goal of the current study was to compare structural grey matter changes of the brain as well as function of the nociceptive system in patients with good and poor outcomes at 6-months following TKA.

Methods

Participants

The study involved a subset of 46 participants from a larger study on the predictors of persistent pain following TKA that included 300 patients with knee osteoarthritis (ANZCTR #12612001089820). Participants from the larger study who also consented to having an MRI scan were contacted at 6-months post-TKA. The participants were divided into two groups based on a pain Numerical Rating Scale (NRS) at this time. Participants with post-surgical pain $\geq 3/10$ on the 11-point NRS on ≥ 3 days per week in the past month were classified as the HIGH_PAIN group and those with pain $< 3/10$ were classified as the LOW_PAIN group. The LOW_PAIN participants must not have had pain $\geq 3/10$ in any part of the body on 3 or more days per week in the last month or any pain lasting more than 2 hours over the course of the day. This cut-off score was chosen because scores ≥ 3 represent at least moderate pain for the majority of people (17). Recruitment continued until there were at least 15

participants in each group, as studies with similar number of participants have shown significant differences in brain structure between groups (14, 18-25). Participants were excluded if they had any contraindications to MRI, neurological conditions, or could not communicate in English.

Ethical approval for the study was obtained from the institutional ethics committee (Ethics approval reference number NTY/12/02/014/AM02), with locality approval from the hospital undertaking the TKA surgeries. Informed consent was obtained from all participants prior to involvement in the study.

Protocol

Participants underwent a structural MRI scan to study brain areas involved in nociception. Immediately following the MRI scan, QST was performed to provide a functional assessment of the sensory and nociceptive systems. The participants had undergone the same QST assessments approximately one week prior to their TKA, as part of the larger study examining predictors of persistent pain.

Quantitative sensory testing

Pressure pain threshold (PPT) was assessed on the medial joint line of the replaced knee as well as at a remote site – over the contralateral scapula. The pressure was applied at 30 kPa/s using a handheld pressure algometer (Somedic AB, Sweden) with a 1 cm² digital probe. Participants indicated the onset of pain by pressing a button.

Temporal summation of pain was assessed at the affected knee by applying a punctuate stimulus (von Frey monofilament, 180 g) at 1 Hz for 10 stimuli. Participants provided a verbal pain rating on a 0-100 NRS (anchors from “0” – no pain to “100” – worst pain) in

response to a single punctuate stimulus and following the tenth stimulus, with the difference in pain rating determined as temporal summation.

Conditioned pain modulation was assessed by PPT over the affected knee (test stimulus) before and during immersion of the contralateral hand in iced water (conditioning stimulus). Conditioned pain modulation was defined as the *per cent* change in knee PPT assessed before and during the conditioning stimulus, with negative values indicating an increase in PPT due to pain inhibition.

Each assessment of PPT and temporal summation was conducted three times, and the measurements were averaged using the arithmetic mean.

MRI scans

Scans were performed using a 3T Siemens MAGNETOM Skyra Syngo MR D13 with a 32 channel head coil. A T1-weighted, high-resolution anatomical scans were acquired using a 3D MPAGE sequence with the following parameters: voxel size=0.9x0.9x0.9 mm, 176 slices, repetition time=2,000 ms, echo time=3.48 ms, flip angle=9°, field of view=230 mm, and matrix size=256x256.

MRI processing

Structural MRI data were analysed with FSL-VBM (26, 27), which is a part of the FMRIB Software Library (FSL) version 6.0.1 (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). The images had the non-brain structures removed and were segmented into the grey matter, white matter, and the cerebrospinal fluid. A study-specific template was created including all participants. The individual grey matter images were non-linearly registered to the study-specific template, and "modulated" to correct for local expansion or contraction due to the non-

linear component of the spatial transformation. The modulated grey matter images were then concatenated into a 4D image and smoothed with an isotropic Gaussian kernel with a sigma of 2 mm.

Region of interest (ROI) analysis

The analysis was limited to brain regions that have been previously demonstrated to be involved in nociception and to have altered morphology in patients with chronic musculoskeletal pain, particularly osteoarthritis (13-16, 28). The selected *a priori* ROIs included the: insular cortex, S1, dorsolateral prefrontal cortex (DLPFC), hippocampus, thalamus, basal ganglia (caudate nucleus, putamen, and nucleus accumbens), amygdala, nucleus cuneiformis, and PAG.

The Harvard-Oxford Subcortical and Cortical Structural Atlases were used to create masks of the insular cortex, DLPFC, hippocampus, thalamus, caudate nucleus, putamen, nucleus accumbens, and the amygdala. The Juelich Histological Atlas was used to create the S1 mask. The atlas-based masks were thresholded so that they had at least 50% probability of representing the structure of interest and then binarised. The PAG and nucleus cuneiformis ROIs were created based on the regions used in previous studies (29, 30).

Statistical analyses

Between-group differences in participant baseline characteristics were assessed using a non-parametric unpaired test (Wilcoxon) for continuous variables and a Fisher exact test for categorical variables.

For the QST data, comparisons were made between groups at pre- and post-TKA time periods, as well as within each group between pre- and post-TKA using non-parametric Wilcoxon-Mann-Whitney and Wilcoxon tests.

Given the strong association with age and sex and their non-normal distribution, PPT values were also log-transformed and entered into a binomial regression model with group allocation (HIGH_PAIN vs LOW_PAIN) as an outcome variable and the log-transformed PPT value, age, and sex as explanatory variables.

For the VBM data analysis, the comparison between the HIGH_PAIN and the LOW_PAIN participants was performed with the group allocation as the only explanatory variable, as well as with the group allocation and age and sex as covariates of no interest. Associations between the grey matter and QST measures were investigated for log-transformed knee PPT, log-transformed scapula PPT, temporal summation, or conditioned pain modulation. The model included the QST scores as well as age and sex as covariates of no interest, because of the strong effect of age and sex differences on QST (31) values and VBM measures (32-34). VBM analyses were performed using a permutation-based non-parametric testing [*randomise*, $n=5000$ permutations, $P<0.05$, corrected for multiple comparisons using threshold-free cluster enhancement (35, 36)] to identify significant clusters within the ROIs.

Sensitivity analysis

Similar to other studies involving unilateral pain conditions (37-40), scans of participants who had a left TKA ($n=21$) were mirrored across the midline, making the left hemisphere the hemisphere contralateral to the replaced knee for all participants.

Results

Clinical and QST data

There were 31 participants in the LOW_PAIN group and 15 in the HIGH_PAIN group. The groups did not differ in age, gender, side of TKA, body mass index, time between the surgery and the follow-up assessment, and cold water temperature used for the conditioned pain modulation test (Table 1).

Before the TKA, the LOW_PAIN group had a significantly lower NRS pain rating ($P=0.027$) but there were no significant differences in QST measures between the two groups (Table 2).

After the TKA, the LOW_PAIN group demonstrated a larger reduction in pain NRS values ($P<0.001$) and a smaller reduction in scapula PPT ($P=0.043$), but the latter effect did not reach significance ($P=0.18$) when adjusted for age and sex using a binomial regression model. There were no differences in changes in PPT over the affected knee (Wilcoxon test: $P=0.143$ and binomial regression: $P=0.408$) or over the scapula ($P=0.18$). Both groups showed a significant reduction in temporal summation post-TKA but the post-TKA values were similar between the groups ($P=0.415$). A significant increase in conditioned pain modulation was present in the HIGH_PAIN group but, despite lower CPM values post-TKA in this group, they were not significantly different from post-TKA values in the LOW_PAIN group ($P=0.122$), possibly due to high variance in this measure.

MRI data

In comparison with the LOW_PAIN group, patients in the HIGH_PAIN group (controlling for age and sex) had more grey matter in the right nucleus accumbens, right amygdala, and PAG and less grey matter in the dorsal part of the left caudate nucleus (Figure 1 and Table 3). These differences were also significant in a model only with group allocation, without age

and sex as covariates. Temporal summation of pain, adjusted for age and sex, correlated positively with grey matter in the right amygdala, right insula, left caudate nucleus, and PAG (Table 4). There were no regions that demonstrated positive correlation with conditioned pain modulation; negative correlation was observed bilaterally in the caudate nucleus as well as the right putamen and thalamus (Table 4). The PPT over the knee and over the scapula correlated positively with the grey matter volume in the nucleus cuneiformis. There were no other significant correlations.

Sensitivity analysis

When the analysis was repeated on images that were mirrored along the x-axis, so that the right side was ipsilateral to the affected knee, patients in the HIGH_PAIN group had more grey matter in the PAG ($P=0.0458$) and the nucleus cuneiformis ($P=0.049$). The difference in the ipsilateral amygdala was not significant when corrected for age and sex ($P=0.093$). Patients in the HIGH_PAIN group had less grey matter in the contralateral caudate ($P=0.0436$).

Temporal summation of pain correlated positively with grey matter in the ipsilateral caudate ($P=0.0402$) and ipsilateral nucleus accumbens ($P=0.0328$). Knee PPT correlated positively with grey matter in nucleus cuneiformis ($P=0.0242$) and negatively with grey matter in the contralateral amygdala ($P=0.0136$). PPT over scapula correlated positively with the ipsilateral S1 ($P=0.0128$).

Discussion

The most novel element of this study was the comparison of cerebral grey matter structure and nociceptive system function between people with low pain and persistent high pain at six months after TKA. Those with persistent high pain after TKA had a significantly higher

density of grey matter in the right amygdala, right nucleus accumbens, and the PAG, as well as lower grey matter density in the dorsal part of the left caudate nucleus. Interestingly, patients in the high pain group also had higher pain ratings prior to surgery.

While VBM analysis does not provide any information about the nature of the structural changes, a decrease in grey matter may reflect neuronal or glial cell loss, or a reduction in the size of neuronal or glial cells. An increase in grey matter may reflect an increased number or size of neuronal cells, glial activation or an increased number of glial cells, or altered synaptic pruning or formation of new synaptic connections. Structural changes observed in chronic pain may reflect irreversible neurodegeneration (41), reversible changes (15), or neuroplasticity (20).

The right amygdala had higher grey matter density in patients with high pain, but this was not significant after mirroring the images along the x-axis. This suggests that the changes involve the right amygdala rather than the amygdala ipsilateral to joint replacement. The amygdala is activated by noxious stimuli and there is a right-hemispheric lateralisation of pain response with stronger activation to inflammatory and chronic pain on the right; however, the mechanisms of this lateralisation are not fully understood (42). The amygdala is thought to contribute to the transition to chronic pain through its involvement in the consolidation of painful or stressful memories (43). In a rat model of neuropathic pain, lesioning the amygdala prior to nerve injury impeded the development of persistent pain, supporting a key role of the amygdala in pain chronicity (44). Furthermore, Neugebauer et al. (45) showed that experimentally induced knee arthritis lead to widespread synaptic potentiation and enhanced excitability within the amygdala that was maintained even in the absence of continuous afferent input from the painful joint. In our study, amygdala density

was found to correlate significantly with temporal summation of pain, in that those with a higher density had a more sensitised nociceptive system, supporting a relationship with nociceptive processing. Notably, Kulkarni and colleagues (46) reported greater amygdala activation during activity-related knee pain compared to experimentally-induced pain in people with knee OA, highlighting the amygdala's specific role in arthritis-related pain.

The increase of grey matter in the PAG may reflect central sensitisation, as the density correlated with temporal summation of pain. Another brainstem nucleus, the nucleus cuneiformis correlated positively with pressure pain threshold, reflecting higher density equated with reduced sensitivity to pressure pain, both over the involved knee and over the scapula. This may reflect different role of these brainstem nuclei in chronification of pain. Schmidt-Wilcke and colleagues (20) have previously reported a negative correlation between brainstem grey matter and pain intensity.

The changes in the striatum are interesting as there was more grey matter in the right nucleus accumbens in patients with high pain but at the same time there was less grey matter in the dorsal part of left caudate. However, the more ventral part of the caudate nucleus correlated positively with the temporal summation. The dorsal part of the caudate nucleus shows predominant connectivity with the DLPFC and premotor cortex responsible for action planning and execution, whereas the ventral part of the caudate nucleus connects to the medial prefrontal and orbitofrontal cortex involved in the motivational aspect of processing (47) as well as pain chronification (48). Reduced grey matter density in the striatum contradicts findings from previous studies that reported an increase in the striatal grey matter in patients with rheumatoid arthritis (28) or people with genetic predisposition to rheumatoid arthritis (49). However, if the changes in the striatum reflect inflammatory

changes (49) rather than disruption of motor-feedback and motor planning by pain (28), it is plausible that reduced grey matter in the dorsal part of the caudate nucleus in those with persistent pain may indeed reflect changes related specifically to chronic pain (16).

The finding that higher pain before surgery predicts pain after surgery is in line with earlier studies in persistent postsurgical pain in general (50) as well as specifically following TKA (51) (52). Although it was not a goal of study to identify pre-surgical differences between groups, these findings support the idea that those with greater pre-operative pain are likely to have amplified central nociceptive processing, and that this may contribute to ongoing pain following replacement of the joint (52).

This study is not without limitations. The borders of subcortical structures are hard to define and, therefore, there may be some signal contamination within the regions analyzed. There were no comparisons available to pre-surgery MRI scans so it was not possible to determine if the differences in density were present prior to TKA or developed afterwards. We did not obtain assessments of psychological variables, such as catastrophizing, anxiety or depression. It has been shown, for example, that people with post-traumatic stress disorder have altered density of the amygdala (53), indicating these are potential moderating factors. Finally, we did not have a comparative group without knee osteoarthritis. Our primary comparison of interest was between people who developed post-surgical pain and those who did not, thus a control group who had not had knee osteoarthritis or a joint replacement was not deemed necessary.

In conclusion, we have provided a novel analysis identifying structural and functional adaptations of the nociceptive system that are associated with the maintenance of pain following TKA. Morphometric analysis of structural brain data acquired at 6-months after

TKA shows higher grey matter density in the right amygdala and midbrain in those who have persistent pain. As the amygdala plays an important role in pain-related fear, memory, and threat perception, it may contribute to the development of persistent pain after surgery. Alterations in midbrain regions may reflect central sensitisation and chronification of pain, given the significant associations with nociceptive processing measures. Further investigation of these relationships is relevant given the high number of patients who continue to suffer from persistent pain following TKA.

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Conflict of interest

The authors report no conflicts of interest.

Figure legends

Figure 1. Results of voxel-based morphometry (VBM) analyses between the HIGH_PAIN and LOW_PAIN group, adjusted for age and gender, within ROIs with significant effects. There was a significantly larger grey matter density in the right amygdala, right nucleus accumbens, and PAG in the HIGH_PAIN group compared to LOW_PAIN, and the opposite effect in the dorsal part of the left caudate nucleus.

Between-group differences are represented as statistical maps thresholded at $P=0.05$ with a larger grey matter density in the HIGH_PAIN group in red and a smaller grey matter density in the HIGH_PAIN group in blue. Images are presented according to neurologic convention, with right hemisphere structures shown on the right.

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