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Functional and structural neuroplastic changes related to sensitization proxies in patients with Osteoarthritis: a systematic review

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Abstract

Objective: Several reports in literature have identified sensitization as a possible basis for the enhanced pain reactions associated with Osteoarthritis (OA). The aim of this current systematic review is to summarize functional and structural brain changes associated with surrogate sensitization parameters assessed in patients with OA-related pain.

Design: Systematic review.

Subjects: Patients with OA related pain.

Methods: A literature search was conducted systematically in MEDLINE, CINAHL, EMBASE databases for human studies up to December 2019. Articles were included if they assessed brain imaging and senzitisation parameters (quantitative sensory testing and questionnaires) in adults with OA related pain. Methodological quality was assessed using the Methodological Index for Non-Randomized Studies (MINORS) score.

Results: Five studies reporting on 138 patients were included in this review. The MINORS scale yielded mean scores of 8.5/16 and 12.3/24, for the cohort and case-control studies respectively. Four low-quality studies suggest a greater pain matrix activation associated with clinical measures of sensitization in patients with OA, while another study underlined the presence of structural changes (reduced gray matter volume) in the cortical areas involved in the nociceptive processing possible also related to sensitization.

Conclusion: This review shows conflicting evidence for structural and functional neuroplastic brain changes related to sensitization proxies in patients with OA.

Keywords: Osteoarthritis; sensitization; pain; brain imaging; MRI; fMRI.

Introduction

Understanding and managing osteoarthritis (OA) pain is challenging given the several OA phenotypes, differentiated clinical presentations, and the sensory and psychological factors that modulate pain (1, 2). The socioeconomical burden of the OA is growing with about 300 million people affected around the world. The incidence of OA has risen 60% since 1990 (3) with a 31.4% increase in incidence during the period 2007 to 2017. This epidemiologic transition led to growing interest in the study of the sequelae related to OA pain and the mechanism involved in its generation and maintenance (4).

OA symptoms are often considered the results of the chronic overload and impaired biomechanics of the joint which in parts may lead to destruction of the articular cartilage and eventually inflammation. Latest evidence, about the pain-structure relationship in mice, has shown that loading induces an initial stress reaction in the joint and local inflammation, but these processes are not directly responsible for the nociceptive phenotype observed in mice (5). Human radiographic measures of pathologic joint changes have shown modest associations with clinical pain in patients with OA (6). Supporting this, OA patients may be divided in subgroups constructed by dichotomizing clinical knee pain scores and OA grade scores, revealed heightened pain sensitivity in the high pain/low OA grade group, while the low pain/high OA grade group can be less pain sensitive (7).

Recent evidence suggests that this discrepancy may be explained by the propensity of some patients to develop sensitization (8-10). In conditions, such as fibromyalgia, low back pain, tension type headache and persistent pelvic pain, aberration in pain processing mechanisms have been investigated as the basis of chronic pain maintenance (11-14). Proxies of central mechanisms have shown to be manifested across many chronic pain conditions (15) including patients with OA (16). Strong evidence for pain sensitization was reported in a recent systematic review and meta-analysis about the manifestations of pain

sensitization in people with knee OA based on meta-analyses of quantitative sensory testing (QST). The analysis indicated that the pain reported by people with knee OA in those studies was associated with one aspect of QST, pressure pain thresholds (17).

Combinations of QST tools can provide a battery for assessing pain threshold, responses to repeated noxious stimuli and evaluation of sensitivity through mechanical, chemical, electrical, and/or thermal testing, (9, 18) and have been suggested as proxies for individual aspects of the manifestations of sensitization. For example, a person with OA may have reduced thresholds to pressure pain (i.e. more sensitive) locally at the affected joint compared to a pain-free individual and similar thresholds at other body sites. This could be interpreted as peripheral (local) sensitization. If the person with OA has reduced thresholds at the affected joint and reduced thresholds at other body sites, this might be considered a result of additional central changes. Other more dynamic QST assessments of facilitatory and inhibitory processes provide additional insight to levels of sensitization. QST has revealed marked heterogeneity in nociceptive facilitation and inhibition in patients with OA, suggesting that different adaptations of the nociceptive system are present even within the same condition (19). Despite these findings, few studies have investigated if brain-related measures may possibly be connected to facilitated nociceptive processing and/or joint structural changes.

Several neuroimaging studies have discussed the role of specific brain regions in the sensory, affective and cognitive aspects of pain experience (20). Structural and functional magnetic resonance imaging (MRI) may provide data on key central neural adaptations and assist in identifying subgroups OA might and possibly those susceptible to the development of severe chronic pain (21) or chronic postoperative pain after surgery (22). A systematic review on fibromyalgia investigating both functional and structural changes in the brain related to sensitization parameters found conflicting evidence for decreased gray matter

volume in specific brain area and showed an increased activation in the pain matrix (cerebellum, insula, anterior and posterior cingulate, inferior parietal lobe and primary and secondary somatosensory cortex) related to central sensitization in patients with fibromyalgia (23). Such a review has not been performed to identify potential brain-related changes in people with OA-related pain.

The aim of this current systematic review, therefore, is to summarize functional and structural brain changes associated with surrogate sensitization parameters (e.g. QST) assessed in patients with OA-related pain.

Method

This is a systematic literature review of studies investigating or reporting neuroplastic changes related to sensitization proxies in patients with OA. PRISMA guidelines were followed during the design, search and reporting stages of this systematic review. The protocol for this systematic review was registered on PROSPERO (CRD42020156007).

Systematic Literature Search

Our literature search aimed at identifying all available studies that evaluated brain changes related to clinical manifestations of sensitization in the OA population. Electronic literature searches were conducted in the following databases from their inception until December 2019: MEDLINE, CINAHL and EMBASE. Additional records were searched through other sources to complement the database findings; for example, manual searches of reference lists of relevant literature reviews and indexes of peer-reviewed journals were used. Two authors (P.P. and S.M.) performed the search and evaluated the abstracts independently for potential eligibility and subsequently full-text publications for eligibility. A third author (J.H.V.) resolved discrepancies. Each researcher reviewed the title and abstract of all the articles, selecting the relevant ones according to inclusion and exclusion criteria. The references list of each article was also screened in order to find any additional original articles.

Population

The participants in the selected studies had to be adults (18 years of age or older) with a diagnosis of symptomatic OA (osteoarthritis pain)

Exposure

Sensitization. Clinical assessment tools such as questionnaires and/or relative sensory function differences using QST. QST aimed at assessing threshold ratios, provoked

hyperalgesia/allodynia, temporal summation (wind-up like pain), spatial summation, reflex receptive fields, descending pain modulation and referred pain areas were included.

Comparator

People with OA and sensitization compared to 1) people with OA and no sensitization, 2) pain-free people.

Outcome

Structural and functional MRI. For this aim, the search strategy included: neuroimaging OR functional neuroimaging OR Brain imaging OR fMRI OR rs-fMRI OR Voxel-Based Morphometry OR VBM.

Study selection

The search included observational studies (cohort studies, case–control studies and case series) with human subjects and without restrictions regarding date of publication. The decision to include case series was taken because from the beginning of the review we expected few papers to be included and given the objective of summarizing the literature on this topic could be useful to consider this type of studies. We excluded from the analysis all repeated articles, case reports, letters to editor, pilot studies, editorials, technical notes and review articles. Also *in vitro*, preclinical and animal studies were excluded. The participants in the selected studies had to be adults (18 years of age or older) with a diagnosis of symptomatic OA (osteoarthritis pain).

Data extraction

All relevant articles from the aforementioned datasets were identified by two reviewers (P.P. and S.M.) who conducted the data extraction independently. A third author (J.H.V.) resolved discrepancies. Reviewers were not masked to any pieces of information regarding the authors, the journal or the outcomes for each article reviewed. A standardized

form was used to extract data concerning study design, number and mean age of participants, year and country of publication, setting, brain area involved, follow-up timing, clinical outcome measures and reported findings. The form was developed according to the directions of the *Cochrane Handbook for Systematic Reviews of Interventions* − Version 5.1.0. This form was pilot-tested for reliability using a representative sample of the studies to be reviewed.

Quality assessment

The methodological index for non-randomized studies (MINORS) was used to assess the risk of bias and the methodological quality of the included studies(Slim et al., 2003) (24). This scoring system includes eight items for non-randomized studies and four additional items for comparative studies. Each item is scored between 0 and 2, and the maximum possible score is 16 and 24 for non-randomized studies and comparative studies, respectively. Two authors independently answered the questions with 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). Any disagreement was resolved by discussion, and if consensus was not reached an external review author was consulted and then, a decision was made.

Data analysis plan

We planned to perform a systematic review by descriptively presenting the results of the retrieved studies. A meta-analysis was not planned because the main objective of the study was to perform a descriptive analysis to present a state of the art of the topic with the aim of stimulating research in this area.

Results

Study selection

Initially, 1676 studies were identified through database searching. After removing duplicates and screening titles and abstracts of all remaining unique articles, 14 full-text articles were assessed to verify their eligibility for the inclusion in the present study. Nine of these manuscripts were excluded (N= 8 articles did not clinically assess sensitization; N=1 Brain imaging not specifically for pain). Thus, five studies were finally selected for this review (**Figure 1)**. A total of 146 patients with OA (113 knee OA, 20 hip OA and 13 hand OA) and 67 healthy subjects were included in these studies. The basic characteristics of the included studies are summarized in **Table 1**. The type of the included studies were 3 case−control studies (19, 25, 26) and 2 cohort studies (27, 28). The five included studies were conducted in Europe (4) and Oceania (1) and published from 2009 to 2019.

Risk of bias within and across the studies

The MINORS Scale was used to score cohort studies and case−control studies, which yielded mean scores of 8.5 out of 16 and 12.3 out of 24, respectively **(table 2)**. In general, the cohort (2) and case−control (3) studies were of poor quality. In five of the included studies, there was a discrepancy between outcomes listed in the method section and the result section and/or an unclear definition of outcomes in the study.

Data from studies

Association between cortical structure and sensitization proxies

Lewis et al.(19) investigated brain structure in people with knee OA before and after total knee arthroplasty (TKA) and the relationships between these findings and QST (pressure pain threshold, temporal summation to repeated pressure stimulation and conditioned pain modulation). Twenty-nine patients with knee OA were compared with 18

pain-free subjects at presurgical baseline and 6 months following surgery. Brain structure was assessed through MRI Voxel based morphometry (VBM) and the QST was considered the nociceptive system outcome. Before TKA, there was reduced gray matter volume in areas associated with nociceptive processing, compared with the control group. In the longitudinal comparison of the knee OA group, the bilateral amygdala, contralateral hippocampus, and contralateral periaqueductal gray (PAG) were significantly larger at postsurgical time compared with presurgical (peak P-value <0.05). There were no areas that were significantly larger in presurgical OA patients compared with healthy controls, while healthy subjects shown significantly larger gray matter areas bilaterally in the Nucleus Accumbens and Amygdala and in the ipsilateral primary somatosensory cortex compared with presurgical OA patients (peak P-value <0.05). A significant relationship was found in a partial correlation between MRI and clinical variables in the knee OA group before surgery: a larger ipsilateral primary somatosensory cortex volume was associated with a lower knee pressure pain threshold on the knee (p=0.006). VBM analyses indicated that the pain-free subjects had larger gray matter volume bilaterally in the nucleus accumbens, amygdala and in the ipsilateral primary somatosensory cortex compared with preoperative OA patients. The MINORS quality score of the study was 14/24.

Association between cortical activation and sensitization proxies

Pujol et al. (27) studied pain sensitisation in patients with knee OA. Based on the evidence for spreading sensitization to a pressure stimulus modality and temporal summation to repeated pressure stimulation, 60 patients with knee OA were stratified into non-sensitised (27 participants) and sensitised (33 participants) groups and assessed in a single screening at baseline; 24 control subjects without pain or OA were evaluated to compare the results. fMRI was used to assess the evoked brain response during 3 tests (T): T1, pressure

stimulation on the articular line; T2, pressure stimulation on the anterior surface of the tibial region; T3, during a painful heat stimulation on the forearm. The PainDETECT score and specific pain assessment (spreading sensitization and temporal summation) was considered for nociceptive system assessment. No significant differences in brain activation during T1 between sensitized and non-sensitized patients were found. Across the whole patient sample, brain activation during T2, correlated significantly with clinical measurements of pain sensitization. No significant differences in brain activation during T3 between sensitised and non-sensitised patients and between patients and control subjects were found. T3 did not discriminate the sensitization phenomenon. T1 robustly activated all of the neural elements typically involved in pain perception. T2 evoked greater activation in sensitized patients in regions typically involved in pain perception. T3 evoked a pattern of brain activation mostly involving bilateral frontoparietal opercula, insula and basal ganglia. Activations were also identified in the medial frontal cortex and premotor cortex. The quality score of the study was 9/16.

Sofat et al.(26) assessed if sensitization mediates pain perception in hand OA. Thirteen patients with hand OA were compared with 13 pain-free subjects in a single session. fMRI was used to assess brain evoked response to pain induced by a finger flexion-extension (FFE). QST was used assess for signs of sensitization (assessed as the reduced pressure pain threshold) in the considered hand OA patients in a previous published study (Wajed et al., 2012) (29) on the same cohort. Analysis of fMRI data showed increased activation in the thalamus, cingulate cortex, frontal and somatosensory cortex ($p<0.05$) during FFE in the group with hand OA compared with pain-free subjects. Regions of activation were mapped to Brodmann areas 3, 4, 6, 9, 13, 22, 24 and 44. The quality score of the study was 11/24.

Gwilym et al. (25) investigated the supraspinal influences that underlie clinical manifestations (assessed as punctate stimulus detection threshold, punctate hyperalgesia, change in thermal perception thresholds and thermal pain threshold level) that could be considered indicative of possible sensitization. Twelve patients with hip OA were compared with 12 pain-free subjects in a single session. fMRI was used to assess evoked brain responses during punctate and cold stimuli. The PainDETECT score and QST were considered the nociceptive system assessments. Patients were found to have significantly lower threshold perception to punctate stimuli and were hyperalgesic to the noxious punctate stimulus in their areas of referred pain ($p<0.001$). fMRI data illustrated significantly greater activation in the brainstem of patients with OA in response to punctate stimulation of their referred pain areas compared with healthy controls, and the magnitude of BOLD response of this activation positively correlated with the extent of neuropathic-like elements to the patient's pain, as indicated by the PainDETECT score. There were no significant differences in activations of patients versus controls in response to the cold stimulus. Considering the whole brain, increased activity in the PAG in response to punctate stimulation of the referred pain area was detected in patients with OA ($p<0.05$). Considering punctate stimulation, the analysis between groups revealed greater activation in the OA group in the following regions: the anterior cingulate cortex, the right dorsolateral prefrontal cortex, the left middle frontal gyrus, and the left lateral occipital cortex. The quality score of the study was 12/24.

The study of Soni et al. (28) aimed at identifying sensitization using neuroimaging and relating it to arthroplasty outcomes. Twenty-four knee patients with OA, waiting for arthroplasty, were stratified in two groups based on PainDETECT (PainDETECT score <13: nociceptive group; PainDETECT score ≥13: Neuropathic like pain group) and assessed before surgery and at 12 months follow-up. fMRI was used to assess evoked brain response

during punctate stimuli and cold stimuli. PainDETECT and QTS (mechanical pain threshold, cold detection threshold and cold pain threshold) were considered for the nociceptive system assessment. Patients with neuropathic-like pain before surgery (n = 14) reported significantly higher pain in response to punctate stimuli and cold stimuli near the affected joint. Neural activity in patients with neuropathic-like pain, compared to those with nociceptive pain, was significantly lower in the rostral anterior cingulate cortex and higher in the rostral ventromedial medulla during punctate stimulation, with significant functional connectivity between these two areas ($r = 0.49$, $P = 0.018$). There were no areas in which activation was significantly higher in the neuropathic-like pain group than in the nociceptive pain group ($p<0.05$). There was no significant difference in activation in the PAG. The punctate stimuli evoked increased brain activity bilaterally in the secondary somatosensory cortex (S2), anterior and posterior insula, and supplementary motor area, as well as in the mid–anterior cingulate cortex. The cold paradigm was associated with activation in the following areas bilaterally: S2 cortex, caudate, thalamus, cerebellum, and contralateral insula and putamen. The quality score of the study was 8/16.

Discussion

Findings

This systematic review explored the literature about neuroplastic changes in the brain associated or co-occurring with sensitization proxies in patients with OA using specific functional and structural brain imaging. The number of included studies in this systematic review was relatively small (1 structural and 4 functional imaging) and the cohorts of patients likewise small and heterogeneous. The vast majority of the excluded studies did not consider the presence of sensitization and its implication in chronic pain maintenance or were based on clinical case reports and expert opinions, which we excluded from this review. As the quality scores of the included studies were not high and multiple heterogeneous approaches were used, the low quality evidence suggests that conflicting evidence exists regarding a relationship between neuroplastic changes and sensitization in people with OA, and depended on the different methodology employed in the studies.

Neuroplastic changes in the brain areas of patients with OA, associated with sensitization reported in the included studies, were in regions associated with the "pain matrix" (30). The signs of cortical changes in patients that clinically show sensitization suggest that these variations are probably related to central pain mechanisms. However, because of the lack of prospective studies performed in this area of study, it is not possible to establish whether the reported neuroplastic changes were a cause or a result of pain.

MRI and OA: People with OA versus pain-free people.

Several cortical structural and functional differences were identified between people with OA and pain free people in this review. First, pain free people showed significantly greater gray matter bilaterally in affective brain regions (Nucleus Accumbens and Amygdala)

and in the ipsilateral primary somatosensory cortex compared with people with OA awaiting joint replacement surgery. The primary somatosensory cortex is of interest because of its major role in the localization and discrimination of pain alteration (31). Indeed, the neuroplastic changes of this brain area are thought to be one of the causes for chronic pain and not merely a passive phenomenon following tissue/nerve injury as previously assumed (32).

Structural alterations of gray matter is thought to possibly result from plasticity that occurs in the context of structural remodeling and reorganization of synapses, cells and circuits, potentially contributing to the long-term nature of chronic pain (33, 34). Structural brain biomarkers for chronic pain have been reported in literature for other conditions suggesting numerous patterns of structural changes that are specific to several conditions related to pain (35, 36).

Functionally, increased activation in the thalamus, cingulate cortex, frontal and somatosensory cortex occur during movement evoked pain in people with hand OA compared with pain-free subjects (26). These cortical regions are implicated in central sensitization. Additionally, greater activation in the brainstem, anterior cingulate cortex, the right dorsolateral prefrontal cortex, the left middle frontal gyrus, and the left lateral occipital cortex was also reported (25) in patients compared to pain free people in response to punctate stimuli. This activation was correlated with the extent of neuropathic pain symptoms reported by patients.

MRI and OA: People with sensitization versus people without

In the study by Pujol (27), pressure stimulation on the anterior surface of the tibial region (i.e a site remote to the reported painful joint) evoked greater activation "somatosensory cortices, supramarginal gyrus, insula, visual and auditory" areas in patients

classified as “sensitized” compared to the non-sensitized group. Interestingly, the authors indicate that these identified areas overlap with those activated in people with fibromyalgia, a condition associated with primary sensitization. In separate work (28), patients with neuropathic-like pain before surgery reported significantly higher pain in response to punctate and cold stimuli near the affected joint than those without neuropathic pain. Neural activity bilaterally in the secondary somatosensory cortex (S2), anterior and posterior insula, and supplementary motor area, as well as in the mid–anterior cingulate cortex in these patients was significantly lower in the rostral anterior cingulate cortex and higher in the rostral ventromedial medulla during punctate stimulation, with significant functional connectivity between these two areas. Interestingly there was no significant difference in activation in the PAG possibly suggesting that differences in endogenous inhibitory capacity may not have differed between groups.

MRI: structural differences and QST

Lewis et al.(19) explored structural brain changes in patients with OA before and after TKA, showing their relationship with the QST. In particular, they identified a significant correlation between imaging data and clinical PPT such that a larger ipsilateral primary somatosensory cortex volume was associated with a lower knee pressure pain threshold on the knee.

In contrast, an emerging study that analysed the individual difference in sensitivity in a large sample of people in pain strongly suggests an absence of associations between PPT and gray matter volume (37). Previous studies have reported that PPTs at the knee and distant sites are reduced in people with knee OA, and the presence of widespread hyperalgesia and enhanced spatial summation observed as indicative for sensitization (38).

Widespread sensitization was detected also in patients with pain after TKA revision and underlined the importance of ongoing nociceptive input for the chronification process (39).

MRI: function (activation) differences and QST

The observation that several brain areas are activated by transient painful stimuli, and that the magnitude of this activity is often graded with pain intensity, has prompted researchers to extract features of brain activity that could serve as biomarkers to measure the pain matrix activity. An fMRI study by Soni et al.(28) analyzed functionally linked regions associated with pain processing, specifically related to sensitization assessed as mechanical and cold pain threshold and cold detection threshold. These neuroimaging data suggest that a subset of patients with OA possible have sensitization showing up as increased brain activity bilaterally in the secondary somatosensory cortex, anterior and posterior insula, and supplementary motor area, as well as in the mid–anterior cingulate cortex.

Emerging evidence suggests that pain sensitization in people with knee OA may be associated with knee OA symptom severity, although not all patients develop detectable sensitization (40). Pujol et al.(27) studied pain sensitization in knee OA and analysed cortical activation to punctate and cold stimuli and found a significant difference between sensitized and non-sensitized patients. Punctate stimulation on the interarticular line showed similar activation of the neural elements involved in pain perception across groups, whereas the punctate stimulation on the distant site (anterior surface of the tibial region) showed greater activation in sensitized patients. In sensitized patients, a state of hyperexcitability consisting of enhanced responses to noxious stimulation has been shown (41).

Also Gwylim et al.(25) found signs of sensitization in patients with knee OA in response to punctate stimulation of referred pain areas, compared with the response of healthy controls: the magnitude of this activation positively correlated with the extent of neuropathic-like elements to the patient's pain. Sofat et al.(26) in contrast, investigated sensitization (pain thresholds to pressure stimulus modality) in patients with hand OA through fMRI data during flexion-extension of the hand and found augmented activation in the thalamus, cingulate, frontal and somatosensory cortex in the OA group but not in healthy controls. The work by Sofat et. al. (26) is the only included study that assessed brain activation during spontaneous pain (without an external stimulation), observing that their cohort of hand OA patients, who presented relatively high VAS pain scores and lower pressure pain threshold measured by algometers, showed a greater activation in the areas that involve emotion, learning, memory and central pain processing. In a previous study, Parks et al.(42) addressed the differences in brain activity during induced pain (with a pressure-evoked pain stimulus) and spontaneous OA knee pain. They suggested that, for spontaneous pain, the engagement of brain regions involved in emotional assessment is mediated sensitization, while evoked pain presents similar mechanisms in patients with knee OA and healthy subjects (42). Hyperalgesia and signs of sensitization have already been reported in a previous clinical study that analysed the nerve sensitivity of patients with hand OA and investigated pressure pain thresholds on local and distant anatomical sites (43, 44).

Understanding both structural and functional brain adaptations to persistent pain may be useful to define specific OA phenotypes of pain and, subsequently, to assess the impact of different therapeutic/preventive modalities on brain changes. Russel et al.(45) evaluated volumetric changes in brain regions of patients with hand OA treated with centrally acting analgesics, showing no structural differences in the insular cortex or thalamus at baseline

and after treatment. Therapeutic exercise has also been investigated for its possible influence on brain changes in patients with knee OA, highlighting the potential use of neuroimaging biomarkers to predict the intervention effect on pain (46). Exercise has the potential to regulate the motor control system by directly modulating the supplementary motor area function, as well as the dorsolateral prefrontal cortex by shifting attention to movements. Moreover, exercise can influence strengthening cognition and self-regulation through the descending pain modulation system and the brain areas associated with emotion (amygdala) and pain (insula) (46).

Limitations

This systematic review did have some limitations; the majority of the studies that has been included did not report cohorts with consecutive patients and preliminary sample size calculations. Three studies had a single assessment at follow-up and 2 studies had a follow up of 6 or 12 months to evaluate the post-surgical outcomes. The sample size of the included studies was relatively small, thus studies with larger sample sizes are needed to further validate the findings. Classification bias might be present as the criteria for the diagnosis of OA were not well described in the studies. Most of the studies were of low quality. Specifically, no RCTs testing the effect of interventions were identified for this review. All the mentioned biases, along with the retrospective nature of studies, may influence the strength of the results. Additionally, given the heterogeneity in methods we are unable to provide recommendations regarding the most effective combination of imaging and QST approaches to best quantify brain-related changes in people with OA and sensitization.

Clinical and Research Implications

Gaining information on neuroplastic changes and neural “rearrangement” may be a new option to develop multimodal approaches for managing OA, including therapies targeting the cortex and sensitization. The studies included in this review were generally rated as lower quality and had heterogeneous methodology.

Brain imaging provides a method to underline the patterns of neural activity in the human brain and spinal cord, providing foundation for research of the afferent and efferent circuitry in the patient with pain. Future studies should be focused on the thorough definition of the neuroplastic adaptations related to the several phenotypes of pain including sensitization. Defining the variation of neuronal patterns during treatments targeting sensitization proxies should be considered in order to improve the quality of personalized treatment based on pain patient phenotype. The optimal methodology to determine if sensitization in people with OA is related to cortical reorganisation would be longitudinal studies of disease/condition progression and recovery after intervention. Unfortunately these studies are difficult and expensive to perform; however, such studies will be needed to untangle the extent to which cortical reorganization occurs in response to prolonged pain, or if differences in structure and function give rise to prolonged pain and/or sensitization, and to determine if any identified changes are in fact reversible. Alternatively, cross-sectional case-control studies with rigorous designs could provide more information about differences in cortical structure and function. In addition, future studies must consider consistent definitions of sensitization and optimal QST measures used to define such sensitization.

Conclusion

This systematic review shows conflicting evidence concerning the structural and functional brain changes related to assessed sensitization occurring in patients with OA. The tools used and applied as proxies for sensitization vary across studies making direct comparisons of the sensitization aspects difficult. The imaging findings of five low-quality studies suggest a greater pain matrix activation associated to clinical measures of sensitization in patients with OA compared to pain-free subjects and possible reduced gray matter volume in the cortical areas involved in the nociceptive processing. The conclusions have a high risk of bias. It was not possible to make a quantitative analysis aimed at comparing the brain area involved. Future works should consider larger sample sizes and longitudinal study designs should be contemplated in order to determine the chronology of brain alterations in relation to the course of the painful condition as well as to evaluate the effects of pain treatments on neural reorganization in patients suffering from OA with concurrent specific sensitized phenotypes.

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Authors contributions:

All the authors meet the following authorship conditions:

1) Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published.

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Figure Legends

Figure 1. Flow diagram of studies through the different phases of the systematic review

Table 1. Characteristics of included studies.

Table 2. Methodological items for non-randomised studies (MINORS scale)

Table 1. Characteristics of included studies.

Author, yrs	Number of participants	Mean (SD) age	Female Ratio (%)	Affected Joint	Used QST modalities	Type of MRI technique	Country	Design of the study	Length of follow-up	Statistical analysis
Pujol et al. (2017) [27]	84 participants (60 Knee OA and 24 healthy subjects.)	-Knee OA 66.7 (7.8) -Healthy subjects 62.8 (7.7)	-Knee OA 71.7% -Healthy subjects 58.3%	Knee OA	PPT, TS to repeated pressure stimulation	fMRI (BOLD) during: Test 1(T1): pressure stimulation on the articular line. T2: pressure stimulation on the anterior surface of the tibial region. T3: during a painful heat stimulation on the forearm.	Spain	Cohort study	Single screening at baseline.	ANOVA to assess within-group and between-group differences.
Lewis et al. (2018) [19]	47 participants (29 Knee OA and 18 healthy subjects)	-Knee OA 68 (10) -Healthy subjects 71.0 (8.0)	-Knee OA 48.3% -Healthy subjects 61.1%	Knee OA after TKA	PPT, TS to repeated pressure stimulation and CPM	MRI VBM	New Zealand	Case-control	Screening before and 6 months after TKA.	Indipendent t-test to investigate differences between groups for VBM and QST data.
Sofat et al. (2013) [26]	26 participants (13 hand OA patients and 13 healthy subjects)	-Hand OA 61.0 (13.7) -Healthy subjects 52.8 (5.3)	-Hand OA 100% -Healthy subjects 100%	Hand OA	PPT	Evoked brain response assessed through fMRI (BOLD) during a finger flexion-extension.	United Kingdom	Case-control	Single screening at baseline	t-test was performed
Gwilym et al. (2009) [25]	32 participants (20 hip OA patients, 12 underwent fMRI; 12 healthy subjects)	-Hip OA 63.0 (8.0) -Healthy subjects 64.0 (9.0)	-Hip OA 50% -Healthy subjects 45%	Hip OA	punctate stimulus detection threshold, punctate hyperalgesia, change in thermal perception thresholds and thermal pain threshold level	Evoked brain response assessed through fMRI (BOLD) during a punctate stimuli and cold stimuli.	United Kingdom	Case-control	Single screening at baseline	Mann-Whitney test and unpaired t-test was performed
Soni et al. (2019) [28]	24 participants (10 nociceptive pain group and 14 neuropathic pain group)	-Nociceptive group 70.0 (7.0) -Neuropathic group 67.0 (10)	-Nociceptive group, 30.0% -Neuropathic group, 57.0%	Knee OA	mechanical pain threshold, cold detection threshold and cold pain threshold)	Evoked brain response (BOLD) assessed through fMRI during a punctate stimuli and cold stimuli.	United Kingdom	Cohort study	Presurgical baseline and 12 months follow-up assessment.	Student's t-test, Wilcoxon-Mann-Whitney, Fisher's exact test were performed

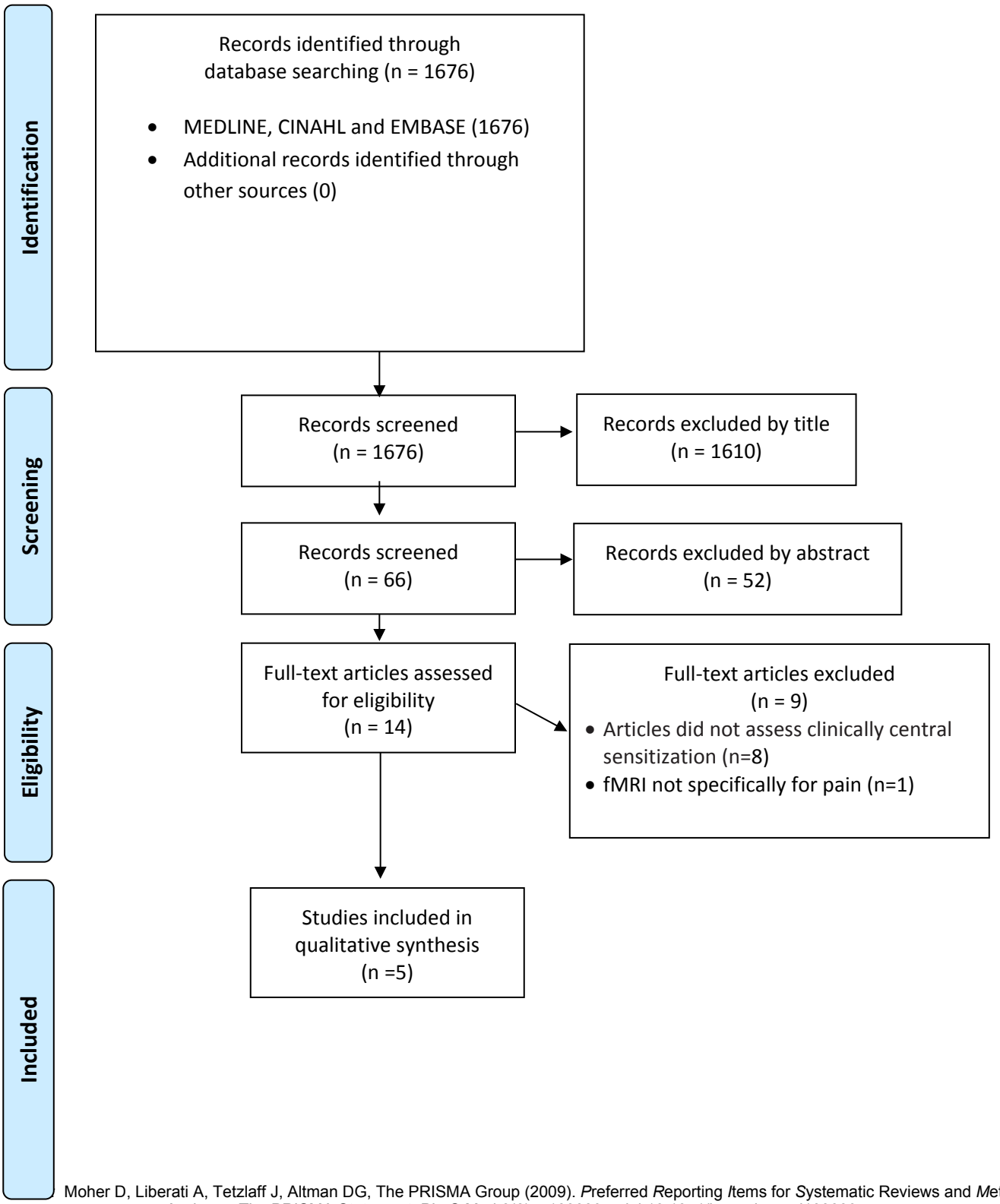
OA: Osteoarthritis**; fMRI:** functional magnetic resonance imaging; **VBM:** Voxel based morphometry; **TKA**: total knee arthroplasty; **QST:** quantitative sensory testing, **PPT**: pressure pain threshold; **TS**: temporal summation; **CPM**: conditioned pain modulation; **BOLD:** Blood oxygenation level dependent.

Table 2. Methodological items for non-randomised studies (MINORS scale)

Authors, Yrs	A clearly stated aims	Inclusion of consecutive patients	Prospetctive collection data	Endpoints appropriate to the aim of the study	Unbaised assessment of the study endpoint	Follow-up appropriate	Loss to follow-up less than 5%	Prospective calculation of the study size	An adequate control group	Contempora ry groups	Baseline equivalence of groups	Adequate statistical analysis	Score
Pujol et al. (2017) [27]	2	2	0	2	1	2	0	0	-	-	-	-	9/16
Lewis et al. (2018) [19]	2	1	1	2	0	1	2	0	1	2	0	2	14/24
Sofat et al. (2013) [26]	2	0	0	1	0	1	0	1	1	2	1	2	11/24
Gwilym et al. (2009) [25]	2	1	1	2	0	1	0	0	1	2	1	1	12/24
Soni et al. (2019) [28]	2	1	1	0	0	2	0	2	-	-	-	-	8/16

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies

Figure. 1 Flow diagram based on PRISMA statement (www.prisma-statement.org, accessed on: 30/01/2020).



Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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