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REVIEW

Evidence for central sensitization in patients with osteoarthritis pain: A systematic literature review

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Abstract

Hyperexcitability of the central nervous system (CNS) has been suggested to play an important role in the chronic pain experienced by osteoarthritis (OA) patients. A systematic review following PRISMA guidelines was performed to evaluate the existing evidence from the literature related to the presence of central sensitization (CS) in patients with OA. Electronic databases PubMed and Web of Science were searched to identify relevant articles using pre-defined keywords regarding CS and OA. Full-text clinical reports addressing studies of CS in human adults with chronic complaints due to osteoarthritis were included and screened for methodological quality by two independent reviewers. From the 40 articles that were initially eligible for methodological quality assessment, 36 articles achieved sufficient scores and therefore were discussed. The majority of these studies were case–control studies and addressed OA of the knee joint. Different subjective and objective parameters considered manifestations of CS, which have been previously reported in other chronic pain conditions such as whiplash or rheumatoid arthritis, were established in subjects with OA pain. Overall results suggest that, although peripheral mechanisms are involved in OA pain, hypersensitivity of the CNS plays a significant role in a subgroup of subjects within this population. Although the majority of the literature provides evidence for the presence of CS in chronic OA pain, clinical identification and treatment of CS in OA is still in its infancy, and future studies with good methodological quality are necessary.

1. Introduction

Osteoarthritis (OA) is one of the most frequent, disabling and costly pathologies affecting modern society. Subjects with OA pain often suffer from chronic pain leading to important disabilities and associated costs for the public health system (Jinks et al., 2007). During the past years, a growing body of research suggests that central sensitization (CS) in OA has been developed (Lluch Girbés et al., 2013). According to Woolf (2011), CS is 'operationally defined as an amplification of neural signaling within the central nervous system (CNS) that elicits pain hypersensitivity'. CS is a broad concept reflecting not only spinal cord sensitization but also enhanced activity of pain descending facilitation pathways (Meeus and Nijs, 2007; Staud et al., 2007), loss of descending antinociceptive mechanisms (Meeus et al., 2008), overactivity in the pain neuromatrix (Seifert and Maihöfner, 2009) and long-term potentiation of neuronal synapsis in the anterior cingulate cortex (Zhuo, 2007). Wind-up, activation of collateral synapses, apoptosis of gABAergic inhibitory interneurons, sprouting of Aβ-fibres in lamina II or glial activation are also important functional changes observed in the CNS with CS (Woolf, 2011).

Database
- PubMed and Web of Science, including full-text clinical reports.

What does this review add?
- Narrative reviews regarding central sensitization in osteoarthritis exist, but there are no studies that systematically reviewed the literature related to the presence of central sensitization in osteoarthritis pain.
- This systematic review provided evidence that the central nervous system becomes hypersensitized in subjects with chronic osteoarthritis pain, and that the phenomenon of central sensitization plays a crucial role in the pain complaints reported by these patients.

Changes that have been associated with CS in OA patients include extended and remote areas of hyperalgesia from the affected joint (O'Driscoll and Jayson, 1974; Kosek and Ordeberg, 2000a; Bajaj et al., 2001; Imamura et al., 2008; Arendt-Nielsen et al., 2010), a loss of descending pain inhibitory mechanisms (Kosek and Ordeberg, 2000a; Arendt-Nielsen et al., 2010; Graven-Nielsen et al., 2012), and an increase of temporal summation (TS) (Arendt-Nielsen et al., 2010) and spatial summation (SS) (Graven-Nielsen et al., 2012). All these changes are recognized indicators of the presence of CS (Graven-Nielsen et al., 2012). Moreover, positive effects of centrally acting drugs (Chappell et al., 2009), use of neuropathic pain descriptors (Hochman et al., 2010, 2011), presence of symptoms suggesting CS (i.e., widespread pain, fatigue, sleep disturbance and cognitive difficulties) in subgroups of patients with OA (Murphy et al., 2011b) and results from several functional brain neuroimaging studies (Kulkarni et al., 2007; Gwilym et al., 2009; Parks et al., 2011) support the role of CS in chronic OA pain.

Currently, however, it remains unclear whether sufficient evidence is available in favour of CS in chronic pain related to OA. Although narrative reviews regarding CS in OA exist (Lluch Girbés et al., 2013), there are no studies that systematically reviewed the literature regarding CS in chronic OA pain. Recent systematic reviews have demonstrated that CS plays a role in other chronic pain conditions, such as whiplash (Van Oosterwijck et al., 2013) and rheumatoid arthritis (Meeus et al., 2012). If CS is dominating the clinical picture of patients with chronic OA pain, then treatment programmes should be adapted accordingly (Lluch Girbés et al., 2013).

Hence, the aim of this study was to systematically review and evaluate the existing evidence from the literature in order to establish if there are enough arguments to support the role of CS in chronic pain related to OA.

2. Literature search methods

2.1 Search strategy

To identify relevant articles concerning central pain processing in patients with OA, a systematic search of the literature using the PRISMA guidelines (Liberati et al., 2009) was performed in databases Pubmed (http://www.ncbi.nlm.nih.gov/sites/entrez) and Web of Science (http://apps.isiknowledge.com) in January 2013. The results for every database and combination of keywords and MeSH terms used in the search strategy are represented in Supporting Information Table S1. In addition, reference lists from relevant articles were checked to obtain as complete information as possible.

2.2 Study selection

Initially, all titles and abstracts of the retrieved articles were screened to identify relevant papers related to CS in OA using pre-defined inclusion criteria. In case of uncertainty regarding appropriateness of the paper after reading title and abstract, the full version of the text was retrieved and checked for fulfilment of inclusion criteria. To be included in the review, an article had to meet all the following criteria: (1) to be reported in a peer-reviewed academic journal; (2) the author(s) studied the phenomenon of CS in human adults (18 years or older) with chronic pain due to OA; (3) the article was a full-text original research report, and not an abstract, letter, editorial or review; and (4) the study was presented in English. No limitation regarding year of publication was used, and all clinical study designs were eligible.

Although review articles were not eligible for inclusion, their reference lists were screened to collect relevant articles that were not initially retrieved by the systematic search. The full-text version of all the articles that met the inclusion criteria were retrieved, and methodological quality assessment and data extraction was performed.

2.3 Quality assessment

To evaluate the methodological quality of the full-text papers, we used a checklist of 18 criteria, which was composed and used previously by Van Oosterwijck et al. (2013) (see Supporting Information Table S2). We chose to use these criteria as they have proven to generate reliable risk of bias scores for papers reporting studies examining the presence of CS in chronic pain patients (Van Oosterwijck et al., 2013). Indeed, the inter-tester reliability of the risk of bias scores was high, reflected by the 96% (416 out of 432 items) agreement in scoring between the two researchers conduct-

ing the systematic review (Van Oosterwijck et al., 2013). The quality criteria were developed by selecting criteria, of relevance to the research question of the literature review, from established risk of bias scoring lists. This is important as the present study addresses a similar research question (i.e., examining whether CS is present in a specific chronic pain population) in a different patient population (chronic whiplash associated disorders vs. osteoarthritis).

Two independent and blinded researchers (E.L. and R.T.) scored the studies and assessed whether each of the evaluation criteria was fulfilled. After rating the selected articles, they compared the results and, in the case of disagreement, the article was screened a second time and the point of difference was discussed. Both reviewers could argue and convince the other to obtain a consensus. When consensus could not be reached, a third researcher (J.N.) was called upon to make the final decision. Besides evaluating the overall quality, articles were categorized according to purpose (aetiology, prevalence, incidence, prevention, treatment, case report, diagnosis) and study design (prospective, clinical trial, hypothetical, cohort, case–control, cross-sectional).

Only those criteria that were applicable for the study design were taken into consideration. One point was given in case a study met with the related criterion, no point in case it did not fulfil the criterion. A total score was calculated as the sum of all the evaluation criteria that was fulfilled and then transformed into a percentage. For example, if only 14 out of the 18 criteria were applicable, and 7 of the 14 criteria were fulfilled, this resulted in a score of 7/14 or 50%. Articles that did not reach the minimum threshold of 40% on methodological quality scoring were not considered in this review.

Finally, the results were analysed and the existing evidence regarding CS in OA were summarized.

3. Results

3.1 Search strategy

The selection process of the articles is represented in Supporting Information Fig. S1. The initial search resulted in 1423 hits. After removal of duplicates, 737 articles remained. Four additional references were retrieved from the reference lists of papers selected. Titles, abstracts and full-text papers, if necessary, were then screened for inclusion criteria fulfilment. After screening, 697 studies were excluded and 40 articles were initially eligible for methodological quality assessment as presented in Supporting Information Table S2.

3.2 Methodological quality assessment

There was a 96.5% agreement (695 of the 720 items) between the two researchers on scoring the selected papers on methodological quality. After a second review, the reviewers reached a consensus in all except for four items. Final decision on these four items was resolved by a third researcher.

Supporting Information Table S2 provides the details regarding fulfilment of the methodological quality criteria for each analysed study. In only 3 out of the 40 studies the sample size was sufficient and justified for (criterion 1). Eight out of the 40 studies did not describe the diagnostic criteria for OA, while 7 research papers did not clearly describe inclusion and exclusion criteria used for patient's selection (criteria 2 and 3). Groups were comparable at baseline regarding demographic data in 29 studies (criterion 5). The validity and reliability of the outcome measures used was only described in 13 out of the 40 studies (criterion 6). Co-interventions were taken into account in 24 studies (criterion 7), whereas only 5 out of the total studies selected included a washout period before starting the study (criterion 8). Subjects were blinded in eight studies, assessor(s) in seven studies and therapist who administered the therapy in three studies, although these criteria were not always applicable. Although three studies performed a double-blinded design (i.e., subjects and therapists), only two studies examined and reported whether the blinding procedure was effective (criterion 12). Eleven studies included a follow-up period (criterion 18).

To be further considered in this review, articles were required to have a score of ≥40% on methodological quality. If this score was not achieved, the study was rejected because of poor methodological quality. Four studies (Gerecz-Simon et al., 1989; Westermann et al., 2011; Wylde et al., 2011, 2012) were excluded for this reason. In conclusion, 36 studies with sufficient methodological quality were considered, and the characteristics and findings of these studies are discussed below.

3.3 Study characteristics

Of the 36 selected studies, most were categorized as case–control ($n = 19$) or cross-sectional studies ($n = 12$). Five research papers were randomized controlled trials. Twenty-two out of the 36 studies investigated the aetiology of OA, 5 were treatment-focused and 5 were classified as mixed aetiology treatment. Only two studies were classified as prevalence studies, and two more as diagnosis studies (Supporting Information Table S3).

OA of the knee joint was examined in 24 studies, while 5 focused their interest upon the hip, 3 on the first carpo-metacarpal (CMC) joint and 3 examined

both hip and knee OA. One study recruited subjects with OA in the lower extremities.

3.4 Evidence for CS in OA

Besides listing the search results and characteristics of included studies, the aim of this systematic review was to summarize the present knowledge on CS in OA. In the following section, the results of this review will be structured according to the different aspects of sensitization, which have been identified in patients with OA.

3.4.1 Clinical manifestations of CS in OA

Three studies inferred CS based upon neuropathic pain descriptors of symptoms (Gwilym et al., 2009; Hochman et al., 2010, 2011). Hochman et al. (2010) qualitatively assessed the OA pain experienced by 80 subjects with knee OA. A small subgroup of patients (i.e., 34% from the total), who used neuropathic pain descriptors, was identified. Those who used neuropathic pain descriptors were mainly young women with high pain intensity, high OA severity and long OA duration. In a later study, a similar percentage of patients reporting neuropathic pain symptoms (i.e., 28% from a total of 171 subjects with knee OA) was found (Hochman et al., 2011). Gwilym et al. (2009) determined that the magnitude of activation in the periaqueductal grey matter of subjects with hip OA after punctuate stimulation of their referred pain areas was correlated with the extent of neuropathic pain symptoms.

Based upon the location of the symptoms (Wood et al., 2007) and a positive correlation between OA pain severity and centrally mediated symptoms (Murphy et al., 2011a,b), some studies indicated a potential contribution of the CNS in subjects with OA.

Wood et al. (2007) found that subjects with knee OA reporting generalized knee pain with radiation had more persistent and severe pain, and higher anxiety levels.

Murphy et al. (2011a) measured pain severity and centrally mediated symptoms in women with knee OA. Age, radiographic severity and centrally mediated symptoms explained 27% of the variance in pain severity reported by the patients. After entering age and radiographic severity as variables, centrally mediated symptoms explained an additional 10% of the variance in pain.

Arendt-Nielsen et al. (2010) showed how the degree of local (i.e., knee) and spreading (i.e., leg, arm) sensitization correlated with pain severity. However, no correlation was found between radiological findings and experimental or clinical pain parameters. Accordingly, Lundblad et al. (2008) demonstrated that elimination of the nociceptive input from the damaged joint (i.e., prosthetic substitution) was not always followed by a complete resolution of symptoms. Interestingly, subjects who reported a high pre-operative score for knee pain and low pre-operative pain thresholds were at increased risk of persistent pain after surgery.

3.4.2 Quantitative sensory testing (QST) results in OA

Seventeen studies in total performed QST analysis as part of their outcome measures (O'Driscoll and Jayson, 1974; Farrell et al., 2000a,b; Kosek and Ordeberg, 2000b; Wilder-Smith et al., 2001; Hendiani et al., 2003; France et al., 2004; Moss et al., 2007; Imamura et al., 2008; Lundblad et al., 2008; Gwilym et al., 2009; Arendt-Nielsen et al., 2010; Lee et al., 2011; Graven-Nielsen et al., 2012; Kavchak et al., 2012; Vance et al., 2012; Finan et al., 2013). Different QST modalities were used for evaluating sensory and pain perception, with the mechanical stimulus being the most common form of external stimulation used (14/17 studies) (Farrell et al., 2000a,b; Kosek and Ordeberg, 2000b; Hendiani et al., 2003; Moss et al., 2007; Imamura et al., 2008; Gwilym et al., 2009; Arendt-Nielsen et al., 2010; Lee et al., 2011; Graven-Nielsen et al., 2012; Kavchak et al., 2012; Vance et al., 2012; Finan et al., 2013). Most of the studies performed QST at local (i.e., on or in close proximity to the joint affected by OA) and distant sites (i.e., remote from the affected joint) (Kosek and Ordeberg, 2000b; Hendiani et al., 2003; France et al., 2004; Moss et al., 2007; Imamura et al., 2008; Arendt-Nielsen et al., 2010; Graven-Nielsen et al., 2012; Kavchak et al., 2012; Vance et al., 2012; Finan et al., 2013).

Several studies reported more local and widespread hyperalgesia in subjects with OA compared to controls (Farrell et al., 2000a; Kosek and Ordeberg, 2000b; Imamura et al., 2008; Arendt-Nielsen et al., 2010; Lee et al., 2011; Graven-Nielsen et al., 2012; Kavchak et al., 2012). In addition, a higher degree of general sensitization was related to higher levels of pain perception (Farrell et al., 2000a; Wilder-Smith et al., 2001; Imamura et al., 2008; Arendt-Nielsen et al., 2010; Finan et al., 2013), disability and poorer quality of life (Imamura et al., 2008), poor prognosis after joint replacement (Lundblad et al., 2008), less radiographic evidence of OA (Finan et al., 2013) and high serum concentration of pro-inflammatory cytokines (Lee

et al., 2011). Improvements of widespread hyperalgesia were reported after surgery (O'Driscoll and Jayson, 1974; Kosek and Ordeberg, 2000b; Graven-Nielsen et al., 2012), mobilization of the affected joint (Moss et al., 2007), transcutaneous electrical nerve stimulation (TENS) application (Vance et al., 2012) and medication (Wilder-Smith et al., 2001).

Allodynia, both locally (Hendiani et al., 2003; Kavchak et al., 2012) and extensively (Kosek and Ordeberg, 2000b), was shown to be present in OA subjects as compared to controls. Hypoesthesia was also higher in patients with OA (Hendiani et al., 2003; Gwilym et al., 2009; Kavchak et al., 2012), but only at the affected joint.

3.4.3 Induced referred pain in OA

Only one study examined the phenomenon of evoked referred pain in subjects with OA (Bajaj et al., 2001). Compared with controls, subjects with OA showed significant higher local pain duration and intensity, larger pain areas and increased referred and radiating pain intensities after intramuscular hypertonic saline infusion.

3.4.4 Altered spinal reflexes in OA

Three studies used the nociceptive flexion reflex (NFR) to investigate possible disturbances in nociceptive processes (Emery et al., 2006; Courtney et al., 2009, 2010). Increased excitability of NFR was found in subjects with chronic knee OA compared to controls (Courtney et al., 2009). In a later study, NFR responses markedly augmented after applying joint compression, whereas joint mobilization (but not sham intervention) reduced NFR excitability (Courtney et al., 2010). Emery et al. (2006) showed an increase in NFR thresholds and a decrease on pain ratings following a 45-min coping skills treatment session.

3.4.5 Enhanced temporal or spatial summation of pain in OA

Two case–control studies reported enhanced TS in subjects with knee OA compared to healthy controls (Graven-Nielsen et al., 2012; Goodin et al., 2013). Goodin et al. (2013) assessed the relation of TS of heat pain with clinical measures such as dispositional optimism, pain catastrophizing and depression. A greater dispositional optimism was found to be associated with less pain catastrophizing and less TS of heat pain.

The only study that showed enhanced SS of pressure pain in subjects with knee OA was conducted by Graven-Nielsen et al. (2012). It is worth emphasizing that they found restoration of SS ratios following knee joint replacement surgery.

3.4.6 Dysfunctional endogenous nociceptive inhibition in OA

Descending modulation of pain has been evaluated through the conditioned pain modulation (CPM) paradigm, which assesses the efficiency of descending pain inhibitory mechanisms. Five studies provided evidence for impaired CPM in subjects with OA (Kosek and Ordeberg, 2000a; Quante et al., 2008; Arendt-Nielsen et al., 2010; Graven-Nielsen et al., 2012). In addition, Kosek and Ordeberg (2000a) and Graven-Nielsen et al. (2012) demonstrated restoration of impaired CPM after surgery. Ischaemic compression of the arm with a tourniquet cuff was used as conditioning stimuli in all (Kosek and Ordeberg, 2000a; Arendt-Nielsen et al., 2010; Graven-Nielsen et al., 2012), except for one study (Quante et al., 2008). Experimental stimuli (dependent variable) consisted of pressure pain (Arendt-Nielsen et al., 2010; Graven-Nielsen et al., 2012), electrical-induced pain (Quante et al., 2008) or a combination of thermal and pressure pain (Kosek and Ordeberg, 2000a).

3.4.7 Dysfunctional opioid and non-opioid mechanisms of pain control in OA

To further unravel the role of CS in patients with OA, two randomized controlled trials evaluated the efficacy of centrally acting drugs (Chappell et al., 2009; Abou-Raya et al., 2012). Abou-Raya et al. (2012) and Chappell et al. (2009) found a significant reduction on pain after duloxetine administration compared to placebo, supporting a role of CS in OA.

3.4.8 Altered cytokine and neuropeptide concentrations in OA

One study highlighted the relationship between central pain processing and the inflammatory response in OA by identifying associations between psychophysical pain measures (i.e., QST) and pro-inflammatory cytokine levels (Lee et al., 2011). Low pressure pain thresholds taken at remote sites from the affected joint and high suprathreshold heat pain ratings were associated with elevate C-reactive protein and IL-6 serum levels (Lee et al., 2011).

Intrathecal and blood concentrations of glial cell line-derived neurotrophic factor (GDNF), interleukin-1β (IL-1β), tumour necrosis factor-α, IL-6, IL-10 and

IL-8 were compared between subjects with OA and controls by Lundborg et al. (2010). Subjects with OA presented higher CNS levels of GDNF and IL-8 than controls, and pain level was associated with high levels of GDNF (Lundborg et al., 2010).

3.4.9 Neuroimaging

Five studies reported alterations in brain function in subjects with chronic OA pain (Kulkarni et al., 2007; Quante et al., 2008; Gwilym et al., 2009; Parks et al., 2011; Howard et al., 2012). Gwilym et al. (2009) observed greater activation in periaqueductal grey matter in OA subjects in response to punctate stimulation of their referred pain areas. In another study, brain activity associated with spontaneous OA pain had a brain representation consisting of the prefrontal-limbic region, which is a brain region known to be involved in emotional self-assessment (Parks et al., 2011). Areas involved in the processing of fear, emotions, aversive conditioning and motivational responses (i.e., medial pain system of the brain) showed increased activity with positron emission tomography (Kulkarni et al., 2007). Quante et al. (2008) observed a decreased activation of the cingulated gyrus during provoked OA pain. Lastly, another study paid attention to patterns of regional cerebral blood flow changes in subjects with first CMC joint OA (Howard et al., 2012). An increase in regional cerebral blood flow in brain areas related to the evaluation of threat to the body from ongoing pain and descending modulatory mechanisms was observed.

Only one study conducted by Gwilym et al. (2010) revealed changes in the brain structure in subjects with hip OA. A significant decrease in grey matter volume (i.e., thalamus) was observed, which was reversible after surgery and was accompanied with improvements on pain and function. Although not detected within our search strategy, a recent study by Baliki et al. (2011) reported specific changes in the cortical grey matter in subjects with knee OA using magnetic resonance imaging. Brain re-organization in OA patients was unique to this condition, enabling to differentiate their 'brain signature' from others (chronic back pain, complex regional pain syndrome) with high accuracy.

3.4.10 Psychosocial influences in OA

Three studies considered psychosocial factors related to OA pain (France et al., 2004; Emery et al., 2006; Goodin et al., 2013). Emery et al. (2006) observed more reduction in anxiety levels in women with knee OA compared to men, immediately after a coping skills training intervention, accompanied by an increase of the NFR threshold and a decrease of pain ratings.

Catastrophizing and emotional-focused coping strategies were associated with higher pain and lower pain threshold and tolerance levels locally, but not with NFR (France et al., 2004). Goodin et al. (2013) showed how greater dispositional optimism was associated with less catastrophizing and less TS of heat pain.

4. Discussion and conclusions

The goal of this article was to review and evaluate the existing scientific literature regarding the role of CS in chronic OA pain. Different assessment methodologies were utilized for evaluating the phenomenon of CS, aiming to understand the different changes in pain sensibility observed in this population. Overall results from our systematic review seem to support a key role of CS in chronic pain related to OA.

The term CS is not really 'yes' or 'no' but it occurs at different degrees over a continuum, from a little to a lot. For instance, in some patient populations, CS may be the characteristic feature of the disorder (e.g., fibromyalgia). In others, such in OA, not all patients have CS, but only a subgroup. Although peripheral mechanisms in OA pain are undeniable, our review disclosed a subgroup of subjects (around 30% of OA patients), with CS contributing to their clinical picture (Hochman et al., 2010, 2011; Murphy et al., 2011b). This was corroborated by means of different subjective (i.e., persistent pain complaints, presence of centrally mediated symptoms, neuropathic pain descriptors) and objective parameters (i.e., widespread hyperalgesia and allodynia, enlarged radiation of pain, altered spinal reflexes, abnormal spatial and TS, impaired descending inhibition, enhanced descending facilitation and brain changes). It should be acknowledged that some of these findings (i.e., enhanced TS or reduced pain inhibition based upon QST) provide direct evidence of CS in OA (Arendt-Nielsen and Graven-Nielsen, 2011). However, other findings (i.e., neuropathic pain descriptors, presence of symptoms such as sleep disturbance) are frequently seen but not exclusively in patients with CS so they only offer indirect evidence of hypersensitivity of the CNS in OA. Similar findings about the characteristics of CS have been previously reported in other chronic pain conditions such as whiplash (Van Oosterwijck et al., 2013) or rheumatoid arthritis (Meeus et al., 2012), suggesting that these conditions are bound by the similar mechanism of altered central pain processing.

Modulation of central hyperexcitability occurred after implementation of different locally treatment modalities such as manual therapy (Moss et al., 2007; Courtney et al., 2010), TENS (Vance et al., 2012), joint replacement surgery (O'Driscoll and Jayson, 1974; Kosek and Ordeberg, 2000b; Graven-Nielsen et al., 2012) or medication (Wilder-Smith et al., 2001). This is in line with the acknowledged modulation of CS by peripheral nociceptive input observed in other chronic pain populations (Staud, 2010). Apart from one study (Emery et al., 2006), interventions specifically addressing descending facilitatory (e.g., cognitive-behavioural therapy), or descending inhibitory mechanisms (e.g., exercise therapy), were not identified in the OA literature. More research should examine the effect of treatment modalities and their influence on outcome measures related to CS in OA.

Supraspinal descending facilitatory influences are able to modulate central hypersensibility and influence the results of QST (Zusman, 2002). Only Goodin et al. (2013) assessed the impact psychosocial factors could have on psychophysical measures of CS. More research is warranted to examine the precise influence of psychological factors on the processing of sensory input in patients with OA, and hence to study cognitive-emotional sensitization in these patients (Brosschot, 2002).

Clinical and laboratory methods employed for diagnosing potential involvement of CS in musculoskeletal pain conditions are diverse (i.e., QST, brain imaging techniques, efficacy of centrally acting drugs). All of them assessed the same underlying biological concept (CS), but in its different manifestations related to the different aspects of sensitization (Graven-Nielsen and Arendt-Nielsen, 2013). For instance, widespread hyperalgesia, which is a manifestation of CS, can be assessed quantitatively in a standardized way using sensory tests, such as pressure algometry. The majority of the studies of the current review identified pain hypersensitivity within laboratory conditions, using costly and unattainable equipment for clinicians. Therefore, evidence-based clinical strategies to more readily and systematically identify CS in OA pain are needed (Lluch Girbés et al., 2013).

Although the quality criteria used for assessing the risk of bias of the selected studies has proven to generate reliable data (Van Oosterwijck et al., 2013) and has been used previously to examine the presence of CS in another chronic pain population (Van Oosterwijck et al., 2013), some issues remain. For instance, a wash-out period could be considered a strength or a weakness: having patients wash-out could itself induce CS, depending upon what medications they are using. On the contrary, enrolling only those patients who are able and willing to discontinue medication use can bias the study towards patients with less severe symptoms who are less likely to show CS. These are important considerations for future research in this area.

Based upon the methodological issues identified in the existing studies, future study designs should use a sufficient and justified sample size and report validity and reliability of outcome measures used. Prevention of bias by including a wash-out period before starting data collection is warranted. Finally, description of the blinding procedure is recommended, and a follow-up period should be included to evaluate the role of central alterations in the long term.

Some limitations need to be acknowledged in this review. Firstly, the screening of the literature databases and selection of studies was carried out by only one assessor, which implies that some relevant studies may have been excluded. Still, the methodological screening of the selected studies was conducted by two blinded researchers. Studies assessing the phenomenon of CS in animal models were excluded, based upon the observation that animal models do not closely mirror the human condition (Arendt-Nielsen et al., 2007). Finally, the majority of the selected studies addressed OA of the knee joint. Hence, care must be taken to extrapolate the results of this review to all OA patients.

In conclusion, the majority of the literature reviewed suggests that the CNS becomes hypersensitized in subjects with chronic OA pain, and that the phenomenon of CS plays a crucial role in the pain complaints reported by these patients. However, both clinical identification and treatment of CS in OA is still in its infancy, and more human research with a good methodological quality is warranted.

Author contributions

Systematic search of the literature was carried out by E.L. Selection of the literature based upon the in- and exclusion criteria was performed by E.L., R.T., J.N. and J.V.O. E.L. and R.T. assessed the methodological quality. E.L. drafted the manuscript. R.T., J..N. and J.V.O. critically revised the manuscript for important intellectual content. J.N. and J.V.O. edited the language. All authors discussed the results and commented on the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Flowchart of study selection.
Table S1. Total of hits for every keyword combination that was used at the PubMed and Web of Science search databases.
Table S2. Evaluation scores on methodological quality.
Table S3. Characteristics of the included studies.