## The role of centralised pain in osteoarthritis

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### ABSTRACT

The mechanisms underlying chronic pain states, including osteoarthritis, differ from those underlying acute pain. In chronic pain states, central nervous system (CNS) factors often play a particularly prominent role. In many individuals with chronic pain, pain can occur with minimal or no evidence of ongoing nociceptive input. Medical subspecialties have applied a wide-range of labels to these pain conditions including fibromyalgia, irritable bowel syndrome and interstitial cystitis to name just a few. These same CNS processes can augment or magnify pain when there is ongoing nociceptive input, as in conditions such as osteoarthritis or autoimmune disorders. The hallmark of these 'centrally driven' pain conditions is a diffuse hyperalgesic state identifiable though the use of experimental sensory testing, that has been corroborated by functional neuroimaging. Characteristic symptoms of these central pain conditions include multifocal pain, fatigue, poor sleep, memory complaints and frequent co-morbid mood and anxiety disorders. In contrast to acute and peripheral pain states that are responsive to non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, central pain conditions respond best to CNS neuromodulating agents, such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and anticonvulsants. While osteoarthritis is generally considered a peripherally mediated pain state, a subset of these patients also manifests centrally driven pain characteristics. Thus, osteoarthritis can also be thought of as a "mixed" pain state and this requires a more tailored approach to treatment.

### Overview

Historically, clinicians have considered the majority of pain in osteoarthritis to be to the result of ongoing peripheral nociceptive input (e.g., caused by damage or inflammation occurring in peripheral tissues). In general, when

pain is present there is typically an exhaustive search for the cause of the pain in the region of the body where the individual is experiencing pain (1). However, data suggest that there is not a single chronic pain condition where radiographic, surgical, or pathological description of peripheral nociceptive damage has been reliably shown to be related to which individuals will report pain, or the severity of the pain experience. This phenomenon appears to be largely due to fact that the central nervous system (CNS) sets the gain or volume control on pain processing, and thus the savvy clinician needs to evaluate patients for the presence of both peripheral (e.g., severity of joint damage) and CNS (pain amplification) factors that are playing a role in the patient's pain and other symptoms.

It is increasingly apparent that most chronic pain conditions are actually better thought of as "mixed pain" states meaning that individual patients have markedly different relative mechaniscontributions (peripheral/nocictic eptive and neural) to their pain. Many individuals with significant peripheral nociceptive input present on imaging studies will not experience pain (e.g., as many as 40% of individuals with severe radiographic evidence of osteoarthritis report having no pain), and other individuals without any identifiable peripheral nociceptive input (based on imaging studies) will experience severe pain. This article reviews some of the latest findings in regard to central pain in osteoarthritis. There is a specific focus regarding how clinicians can use information garnered from the history and physical examination to assess which mechanism or mechanisms are most likely underlying the pain of a given patient with osteoarthritis. This knowledge will allow the clinical to better tailor the therapeutic approach. There are at least three different, and often overlapping, pain mechanisms that can be operative in chronic pain

states like osteoarthritis: peripheral/nociceptive, (peripheral) neuropathic, and central neuropathic, or "centralised" pain (Fig. 1). Some experts use the term "neuropathic pain" to refer to any pain of neural origin, whereas others (including the International Association for the Study of Pain [IASP]) reserve this term for conditions where there is identifiable damage to the nervous system. We acknowledge this discrepancy and prefer to use the term "centralised" pain to refer to instance where the CNS (rather than the peripheral nervous system) is prominently involved in maintaining the pain. The distinction between centralised pain and peripheral neuropathic pain (where peripherallydirected therapies such as injections, topical treatments, and/or surgery could be effective, and should be considered) is also important in some pain conditions where this mechanism is prominent (e.g., low back pain).

Although specific diagnoses are noted in Figure 1 as being considered peripheral/nociceptive, peripheral neuropathic, or centralised, these categorisations are meant to indicate that each of the diagnoses has historically been considered in this manner. Again, the emphasis of this article is the crucial point that some individuals with osteoarthritis have evidence that they have centralised their pain and should likely be treated with centrally-acting treatments in addition to (or even instead of) therapies aimed at the periphery.

### Central or centralised pain states

The term "central pain" was originally (and still is) used to describe pain following a spinal cord lesion or stroke that subsequently resulted in pain. In this case "central" refers to the fact that the *lesion* leading to pain occurred within the CNS – either brain or spinal cord. However, more recently, the term centralised has been extended to describe any CNS pathology or *dysfunction* that may be contributing to the development or maintenance of chronic pain.

"Centralised pain" as newly defined has typically been confined to individuals with functional or idiopathic pain syndromes, including conditions such as fibromyalgia (FM), irritable bowel

### Mechanistic Characterization of Pain

Peripheral (nociceptive)	Peripheral Neuropathic	Central neuropathic or "centralized" pain
<ul> <li>Inflammation or mechanical damage in tissues</li> </ul>	<ul> <li>Damage or dysfunction of peripheral nerves</li> </ul>	<ul> <li>Characterized by central disturbance in pain processing (diffuse hyperalgesia/allodynia)</li> </ul>
<ul> <li>NSAID, opioid responsive</li> <li>Responds to procedures</li> </ul>	<ul> <li>Responds to both peripheral and centrally acting pharmacological therapies</li> </ul>	<ul> <li>Responsive to neuroactive compounds altering levels of neurotransmitters involved in pain transmission</li> </ul>
<ul> <li>Classic examples</li> <li>Osteoarthritis</li> <li>Rheumatoid arthritis</li> <li>Cancer pain</li> </ul>	<ul> <li>Classic examples</li> <li>Diabetic neuropathic pain</li> <li>Post-herpetic neuralgia</li> </ul>	<ul> <li>Classic examples</li> <li>Fibromyalgia</li> <li>Irritable bowel syndrome</li> <li>TMJD</li> <li>Tension headache</li> </ul>

Fig. 1.

syndrome, temporomandibular joint disorder, headache and interstitial cystitis (2, 3). Pain syndromes such as these have been shown to be familial/genetic; they strongly co-aggregate in individuals and families (4, 5). Individuals with centralised pain syndromes describe a well-characterised cluster of symptoms consisting of multifocal pain (high rates of current and lifetime history of pain in multiple bodily regions), and co-occurring somatic symptoms (*i.e.*, fatigue, poor sleep, memory problems) (4, 6). In addition, mood and anxiety disorders are frequently comorbid in centralised pain states (7, 8).

In regard to the cluster of somatic symptoms, as well as the higher than expected rates of mood and anxiety disorders, the best supported pathogenic theory for centralised pain states is disturbances in centrally-acting neurotransmitters (e.g., low norepinephrine, GABA and serotonin; high glutamate and Substance P) that have been shown to play a role in pain in these conditions, as well as in controlling sleep, mood, alertness, etc. (4). Clinicians could consider pain and sensory processing as being controlled in a manner very similar to immune function. High levels of pro-inflammatory cytokines, or low levels of antiinflammatory cytokines, can move an individual towards hyperimmune function; similarly, there are neurotransmitters that are known to either increase or decrease pain transmission in the CNS. The analogy of an increased "volume control" or "gain" setting on pain and sensory processing is helpful to understanding this processes and supported by studies from a variety of sources. Similar to primary hypertension, where a variety of processes can lead to elevated systemic blood pressure these disorders represent "primary hypertension of pain and sensory processing pathways". Elevated levels of neurotransmitters that tend to be pro-nociceptive (i.e., Fig. 2, left side) or reduced levels of neurotransmitters that inhibit pain transmission (i.e., Fig. 2, right side) have a tendency to increase the volume control, and drugs that block neurotransmitters on the left or augment activity of those on the right will typically be found to be effective treatments, at least for a subset of individuals with this spectrum of illness.

The arrows shown in Figure 2 indicate the direction of the abnormalities in these neurotransmitter levels (either in the CSF or brain) that have been identified to date in FM. As noted, in FM, there is evidence for increases in the CSF levels of Substance P, nerve growth factor, glutamate, and brain derived neurotrophic factor (BDNF), and low levels of the metabolites of serotonin, norepinephrine, dopamine, and GABA, any of which could lead to an "increase in the volume control" and augmented



### Fig. 2.

pain and sensory processing (9-13). The endogenous opioid system is the only neurotransmitter system studied to date that has not been found to be dysregulated in a direction that would cause amplified pain transmission. Both CSF levels of endogenous opioids and related brain activity by functional neuroimaging appears to be augmented, not reduced (as would be necessary to *cause* augmented pain processing) in FM, which may be why opioidergic drugs do not work well to treat FM and related pain syndromes (14, 15).

# The role of central factors in osteoarthritis

Until recently, osteoarthritis has been viewed primarily as a "disease" due to damage to the cartilage and bone. If that were true, the magnitude of damage or inflammation of these structures should predict pain severity. Yet, population-based studies suggest otherwiseanywhere from 30-50% of individuals with moderate to severe radiographic changes suggestive of osteoarthritis are asymptomatic, and close to 10% of those with moderate to severe knee pain will have normal radiographs (16, 17). While recognised psychological factors do account for some of the variance in pain and other symptoms, this is only to a small degree (18, 19). The failure of peripheral damage, inflammation, or even psychological factors

to explain the presence, absence, or severity of chronic pain in osteoarthritis should not be surprising. To date, in no chronic pain state is there a strong relationship between peripheral factors and the level of pain patients' experience. More and more data support the hypothesis that osteoarthritis is a mixed pain state and that in some individuals CNS factors play an even more prominent role. The fact that central factors may be important in osteoarthritis helps explain the fact that co-morbid somatic symptoms known to be associated with centralised pain states (e.g., fatigue, sleep disturbance) are very commonly present in osteoarthritis, and are not explained by a purely "peripheral" model of this condition (20, 21). Moreover, a few small studies found that osteoarthritis patients display diffuse hyperalgesia to mechanical or heat stimuli (22). For example, Kosek demonstrated that individuals with osteoarthritis of the hip had reduced descending analgesic activity, which partially normalised following hip arthroplasty, suggesting that the central factors were being at least partly driven by peripheral nociceptive input (23). Since that early study, even more have been performed and showed that some individuals with osteoarthritis have lower overall pain thresholds compared to controls, and have less efficient descending analgesic activity (22, 24).

In another series of studies, Gwilym et al. used both experimental pain testing and sophisticated functional neuroimaging procedures to demonstrate evidence of augmented CNS processing of pain in 20 osteoarthritis patients. Then, they showed in a separate study in osteoarthritis patients that thalamic atrophy observed at baseline improved following arthroplasty (25, 26). Lastly, recent randomised controlled trials have shown that compounds that alter neurotransmitters such as serotonin and norepinephrine (e.g., duloxetine, tricyclics) are efficacious in some osteoarthritis patients for improving pain (27, 28). Despite these finding, peripheral factors remain important in osteoarthritis. Neogi et al. in an elegant study demonstrated that in individuals with asymmetric knee osteoarthritis, the pain levels in each knee strongly related to joint space narrowing in the affected knee (29). Overall, the cumulative data suggest that in some individuals central factors are superimposed upon the more traditional peripheral factors which results in the need for a broader and more flexible approach to diagnosis and treatment of osteoarthritis.

A series of recent studies by Brummett et al. (30-32) have demonstrated the importance of co-morbid centralised pain in osteoarthritis in regard to treatment response. These studies examined large cohorts of patients undergoing knee or hip arthroplasty, and examined how the degree of "fibromyalgianess", symptoms measured using the 2011 survey criteria for FM, contributed to responsiveness of osteoarthritis to 1) opioids administered in the perioperative period, and 2) pain improvement following arthroplasty (30, 31). Each study examined cohorts of over 500 individuals undergoing hip or knee total arthroplasty. Patients were assessed preoperatively using validated selfreported questionnaires, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Brief Pain Inventory (BPI), PainDE-TECT, Hospital Anxiety and Depression Scale, Catastrophising subscale of the Coping Strategies Questionnaire, general health information (e.g., ASA Status, preoperative opioid use, BMI, primary anesthetic), and demographic variables. Participants also completed the 2011 survey criteria for FM, which consists of a measure of widespread pain assessed from a body map and 6 questions about comorbid symptoms such as fatigue or trouble thinking (to-tal score = 0-31). The continuous scale, which ranges from 0-31, was used to assess degree of "fibromyalgianess".

In the study evaluating opioid consumption, perioperative opioid usage was converted into oral morphine equivalents. It was shown that for each one point increase on the fibromyalgianess scale, patients took 9 mg more oral morphine equivalents of opioids in the perioperative period. When those taking opioids before surgery were excluded from the analyses, the findings remained statistically significant, with over 7 mg greater oral morphine equivalents of opioids needed in the perioperative period. These studies are amongst the first to show what has long been anecdotally described - centralised pain is less responsive to opioids than is nociceptive pain. In another study, Brummett et al. explored whether centralised pain (as measured using the 2011 survey criteria for FM) was predictive of persistent pain following arthroplasty. Again, the measure of fibromyalgianess was highly predictive of a poor outcome, and this did not just occur in the "tip of the iceberg" in individuals who might meet diagnostic criteria for FM. In the best linear model for change in pain, fibromyalgianess was independently predictive of less improvement in pain. Lower baseline overall pain, higher doses of preoperative opioids, and knee arthroplasty (vs. hip arthroplasty) were also predictive. Similar predictors were seen with the logistic regression of change in pain, with patients 22% less likely to meet the threshold of pain improvement for every 1-point increase on the 31-point scale. In the logistic model of patient global impression of change, patients were 13% more likely to report failure for every 1-point increase on the fibromyalgianess scale. Again, these are amongst the first data to conclusively show that as pain becomes more centralised in individuals with osteoarthritis, it becomes less responsive

## Drugs for Pain Based on Underlying Mechanisms



to surgical procedures - procedures that are obviously aimed at reducing nociceptive input rather than centrally mediated pain responsiveness.

### Discussion

Individuals with central pain states very often demonstrate an altered noxious thresholds (the point at which a sensory experience such as pressure, heat, or sounds become bothersome) for virtually every type of sensory stimulus (33). This can be easily understood by clinicians and patients alike when the phenomenon is likened to "an increased volume control or gain in the brain for any sensory stimuli". Because of this, individuals with FM or other centralised pain states will often note that they find bright lights, noises and odors very bothersome, and this sensory sensitivity could even explain many of the visceral symptoms experienced (e.g., indigestion, heartburn, abdominal pain, urinary urgency and frequency). Sometimes simply highlighting this physiological understanding of pain amplification can be exceptionally helpful to patients, because they feel heard and understood and when they develop new symptoms that follow this same pattern, they are less concerned that "there is something wrong" which would otherwise often trigger a frustrating search for the cause of the new instance of pain. Helping our patients gain this understanding can be a very effective treatment strategy especially when paired with self-management strategies.

Although there are a number of ways to determine pain sensitivity, data suggest that assessing pressure pain threshold (*i.e.*, tenderness to palpation) is the most reliable and reproducible method for identifying individuals with a centralised pain state (34). Quantitative sensory testing is not yet available widely in clinical practice. Instead, a reliable way to assess overall pain threshold is to assess pain thresholds in the hands and arms of patients with osteoarthritis. A rapid examination by applying firm pressure over several inter-phalangeal (IP) joints of each hand, over also over the adjacent phalanges, and then caudally to include firm palpation of the muscles of the forearm including the lateral epicondyle region, is one way to assess overall pain threshold, as well as get additional diagnostic information about the patient. If the individual is tender in many of these areas, or in just the muscles of the forearm, they are likely diffusely tender (i.e., have a low central pain threshold). However, if the individual is only tender over the IP joints and not the other regions, and especially if there is any swelling over these joints, one should be more concerned about a systemic autoimmune disorder (e.g., rheumatoid arthritis, lupus). Alternatively, sometimes individuals are only tender over the phalanges, and in these instances one might suspect a metabolic bone disease or condition causing periostitis (e.g., hypothyroidism, hyperparathyroidism).

### Choosing pharmacological therapy based on the underlying mechanism(s) of pain in osteoarthritis

Figure 3 shows the classes of drugs that seem most effective in different underlying mechanisms of pain. For peripheral/nociceptive, non-inflammatory pain states such as osteoarthritis, treatment guidelines typically recommend first using acetaminophen (even though there is some question regarding whether this drug is effective for use in chronic pain), and then NSAIDs. In addition to the long understood renal and GI side effects of this class of drugs, the more recently recognised cardiovascular side effects are cause for concern in many osteoarthritis patients. Although opioids had previously been thought to be useful for pain refractory to these treatments, the latest meta-analyses of opioids in osteoarthritis challenge this notion, and generally recommend against opioid use.

There are no studies yet in osteoarthritis testing whether the above drugs that work primarily on nociceptive and not centralised pain are less effective in the osteoarthritis patients that have centralised their pain, and/or whether more centrally acting compound would be more effective in this subset of individuals. This has, however, been shown in other chronic pain conditions so we would expect it to also be true in osteoarthritis. These classes of drugs would include older tricyclic drugs, were first shown to be effective in osteoarthritis several decades ago, but which are rarely used because of concerns regarding toxicity. Because of this toxicity, newer drugs that are also likely working by increasing serotonergic and noradrenergic activity, such as tramadol and duloxetine, have been shown to be effective in osteoarthritis and are more commonly used. Another class of drugs that is often helpful for centralised pain or neuropathic pain is the alpha-2-delta calcium channel ligands (pregabalin and gabapentin), which in contrast to duloxetine and tricyclics have never been shown to be effective in osteoarthritis.

Peripheral pain syndromes (including both inflammatory and non-inflammatory peripheral pain, and peripheral neuropathic pain) can also be treated

with topical agents or injections. Injections of corticosteroids, hyaluronic acid preparations (for osteoarthritis in joints that can be injected), agents that ablate nerves, or capsaicin (effective in both osteoarthritis and neuropathic pain) are all therapeutic options. Again these treatments would be expected to work better in individuals who have not centralised their pain than those who have. Non-pharmacological (non-surgical) interventions with broad support include patient education and self-management strategies, low impact aerobic exercise, weight loss if the patient is overweight, use of walking aids and other assistive devices, and thermal modalities (35). There is also some evidence that cognitive-behavioural therapy could be effective in addressing insomnia and other sleep problems frequently observed in osteoarthritis. (36, 37) All in all, interdisciplinary approaches for chronic pain are well-supported and broadly recommended.

### Conclusions

Over the last decade, significant advances in our understanding of pain are finally making the vision of "personalised analgesia" seem within our grasp. By carefully assembling clues from a history and physical examination, clinicians can now begin to identify the sub-sets of individuals with what were once considered purely "peripheral" pain syndromes, and treat these patients with more centrally- than peripherallydirected pharmacological and nonpharmacological approaches.

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