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Autonomic Nervous System Dysregulation and Osteoarthritis Pain: Mechanisms, Measurement, and Future Outlook

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Abstract

Purpose of Review: The autonomic nervous system is an important regulator of stress responses and exhibits functional changes in chronic pain states. This review discusses potential overlap among autonomic dysregulation, osteoarthritis (OA) progression, and chronic pain. From this foundation, we then discuss preclinical to clinical research opportunities to close gaps in our knowledge of autonomic dysregulation and OA. Finally, we consider the potential to generate new therapies for OA pain via modulation of the autonomic nervous system.

Recent Findings: Recent reviews provide a framework for the autonomic nervous system in OA progression; however, research is still limited on the topic. In other chronic pain states, functional overlaps between the central autonomic network and pain processing centers in the brain suggest relationships between concomitant dysregulation of the two systems. Non-pharmacological therapeutics, such as vagus nerve stimulation, mindfulness-based meditation, and exercise, have shown promise in alleviating painful symptoms of joint diseases, and these interventions may be partially mediated through the autonomic nervous system.

Summary: The autonomic nervous system appears to be dysregulated in OA progression, and further research on rebalancing autonomic function may lead to novel therapeutic strategies for treating OA pain.

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Keywords

osteoarthritis; pain; autonomic nervous system; neuro-immune axis

Introduction

Osteoarthritis (OA) causes a maladaptive repair process in articular joints, where cartilage is destroyed, bone remodels in response to altered joint mechanics, and the synovium can become chronically inflamed. Ultimately, these maladaptive responses across the OA joint lead to pain and disability. In fact, OA is ranked as the tenth highest contributor to global years lived with disability, and the prevalence of OA is expected to increase as the population ages [1]. The destructive changes occurring across the OA joint have been described as a disease of the joint as an organ [2], with anabolic and catabolic shifts in joint homeostasis. This perspective is important because, while cartilage degradation has been the classic hallmark of OA disease progression, there is only a weak relationship between severity of cartilage degradation and severity pain [3]. Bone and synovial changes, by contrast, have shown slightly stronger relationships to patient reports of pain and disability, though no joint-level marker of OA pathogenesis as observed on radiograph or magnetic resonance images have proven to be robust predictors of an OA patient's symptom or disability.

In OA, pain can result from multiple complex interactions between biological and environmental factors, and partly due to this, comprehensive treatments for joint pain remain elusive. Current pharmacological treatments for OA are largely focused on alleviating pain with NSAIDs [4]. However, in many OA patients, NSAIDs fail to fully resolve pain [5], and long-term use of NSAIDs can lead to peptic ulcers [6], atrial fibrillation [7], and chronic kidney disease [8]. As OA research has moved beyond a cartilage view of OA pathogenesis, new opportunities to target different sources of pain in the subchondral bone and synovial lining have been generated. However, despite this progress, there remains an incomplete understanding of the generation of OA pain, and often, the 'joint as an organ system' approach can tend to focus entirely on pain sources from the articular joint. For OA pain, physiologic shifts extend beyond the articular joint, where repeated painful signaling can cause remodeling in pain circuitry within the spinal cord and brain. As a more complete understanding of OA pain is created, there are opportunities to develop new therapeutic strategies, both at the articular joint level and beyond the joint.

As outlined by discussions at the 2019 OARSI World Congress on Osteoarthritis [9], there is a need for a paradigm shift to create new solutions for OA treatment. Specifically, the complexity and heterogeneity of OA pain may be better understood when considering OA as a 'whole-body' disease with interactions between multiple organ systems. This perspective has been incorporated to some degree into the study of OA pain circuitry, including evaluation of physiologic shifts in the spinal cord and brain. However, nervous system plasticity may extend beyond pain circuitry. For example, recent reviews provide a framework for autonomic nervous system dysregulation and shifts in neuro-immune communication to contribute to the pathophysiologic progression of OA [10••, 11]. To

expand on this framework presented by Courties *et al*. [10••, 11], this review discusses possible contributions of autonomic nervous system dysregulation to OA pain and where pain circuitry and neuro-immune communication overlap. Additionally, how chronic pain from the OA joint may modulate autonomic functions is described. We also discuss how critical gaps in knowledge of these systems could be addressed through translational efforts in preclinical and clinical research. Finally, we end by discussing how non-pharmacologic pain interventions for OA, including exercise and mind-body interventions, may already be modulating the autonomic nervous system. By better understanding these systems, there is potential to design combinatorial therapies that treat the 'whole-body' of the OA patient.

The Modulation of the Brain-Joint Axis and Autonomic Nervous System due to Chronic Pain and Inflammation

The autonomic nervous system is traditionally thought of as the system regulating automatic actions of organs in the body, including heart rate, blood pressure, and digestion. The system regulates these processes through sympathetic and parasympathetic branches. In addition to these roles, the autonomic nervous system reacts to acute stressors, such as activation of pain-sensing nerve fibers known as nociceptors. Upon receiving a painful nociceptive signal, the sympathetic nervous system activates to cause a shift in the balance of sympathetic to parasympathetic actions on end organs. Conversely, actions of the vagus nerve, the primary nerve of the parasympathetic nervous system [12], are temporarily attenuated by acute nociceptive stimuli [13, 14]. This decrease in vagal nerve signaling generally causes an increase in heart rate, blood pressure, and respiratory rate, while also slowing digestion. The rapid response of the sympathetic and parasympathetic nervous systems is also inter-connected with the hypothalamic-pituitary-adrenal (HPA)-axis [15]. However, the HPA-axis is the slower acting arm of the stress response system. Furthermore, shifts in the HPA-axis will alter systemic levels of cortisol, a stress hormone and endogenous steroid. Due to quality of current evidence, further research is encouraged to answer whether cortisol is increased in OA patients with elevated pain [16].

Following an acute painful stimulus, actions of the autonomic nervous system and HPA-axis allow the body to confront the stressor and rapidly return to homeostasis. However, when the stressor is chronic, like during chronic pain states, multiple neural and endocrine systems can experience plastic shifts in function due to repeated activation of the autonomic nervous system and HPA-axis. These plastic shifts in function result in chronic maladaptive responses including autonomic imbalance and cortisol dysregulation. Importantly, the vagus nerve's control of acetylcholine and cortisol both have potent anti-inflammatory actions; thus, dysregulation of these systems could allow for unchecked sites of inflammation to occur throughout the body. For example, both macrophages and chondrocytes express the α7-nicotinic acetylcholine receptors. When bound by acetylcholine (controlled systemically via parasympathetic activity), the α7-nicotinic acetylcholine receptors inhibit the MAPK and NF-κB pathways [17–19]. Moreover, via the α7-nicotinic acetylcholine signaling pathway and the direct innervation of the spleen by the vagus nerve, vagus nerve activation patterns help to direct the maturation of circulating macrophages in the body (blue line, Fig. 1) [20]. Second, efferent signaling in the vagus nerve also reaches the gut, and via this signaling, the vagus nerve regulates the production and absorption of nutrients and

the diversity of gut microbiota [12]. In fact, this mechanism of the vagus nerve may help explain bidirectional physiologic links between knee OA progression and gut dysbiosis (green path, Fig. 1). For example, altered microbiome has been noted in chronic pain conditions like OA, rheumatoid arthritis, fibromyalgia and chronic low back pain with a disrupted autonomic nervous system noted in all four diseases [21–27]; however, there are currently no data directly relating chronic pain, vagal tone, and OA-like changes in gut microbiota. Ascending signaling from the vagus nerve to the brain can also stimulate sympatho-excitatory regions in the brain (*i.e.* paraventricular hypothalamic nucleus and locus coeruleus), which control norepinephrine release throughout the body [28]. Like cortisol and acetylcholine, norepinephrine has strong anti-inflammatory effects, which have been noted in chondrocytes (purple path, Fig. 1) [29, 30].

It should be noted there is a non-neuronal cholinergic system within the joint, where various joint tissues are equipped with the biological machinery to synthesize, utilize, and degrade acetylcholine [19, 31–34]. While this is not likely to be directly regulated by the vagus nerve and systemic autonomic function, work evaluating this non-neuronal cholinergic system in the joint demonstrates sensitivity of the joint environment to these signals. Moreover, alterations of systemic regulation of acetylcholine, norepinephrine, and cortisol could lead to imbalance in local non-neuronal cholinergic system. Unfortunately, despite the important known role of the vagus nerve in the control of the neuro-immune axis, very little is known about how the vagus nerve and the autonomic nervous system are altered by OA. As such, foundational studies to address how systemic changes in the autonomic nervous system impact the local joint environment's synovium, cartilage, and chondrocyte nicotinic acetylcholine receptors should be undertaken. Likewise, determining how direct modulation of the joint's non-neuronal cholinergic system impacts peripheral and central sensitization mechanisms and autonomic shifts should be pursued. In doing so, the extent of involvement between the non-neuronal and neuronal cholinergic systems within the context of OA will be better understood.

While little is known on autonomic dysfunction in OA, dysfunction of the autonomic nervous has been identified in multiple chronic inflammatory diseases, including Crohn's disease, rheumatoid arthritis (RA), arthrosclerosis, hypertension, and diabetes [35–38]. Decreases to both the parasympathetic and sympathetic components of the autonomic nervous system have been noted in RA patients. For example, RA patients present with attenuated high-frequency heart rate variability (a measure of cardiac vagal tone and parasympathetic function [39]) and reduced low-frequency heart rate variability (a measure of sympathetic function [40]). Consistent with this, α7 nicotinic acetylcholine receptor knock-out mice with collagen-induced inflammatory arthritis have higher clinical arthritis scores, a higher degree of joint damage, and increased levels of circulating pro-inflammatory cytokines compared to wildtype controls [41]. Interestingly, the Lewis rat has known dysfunction of the HPA-axis, which leads to reduced ability to respond to inflammatory insult and increased susceptibility to inflammatory arthritis [42]. We recently showed some changes in cardiovascular function in male Lewis rats with knee OA, which suggest autonomic dysfunction with OA [43]. As such, there is a growing body of evidence for autonomic dysregulation related to joint inflammation, be that OA or RA. The growing

evidence for autonomic dysregulation in RA models suggests a clear opportunity to evaluate the extent of autonomic dysregulation occurring with OA.

In addition to OA inflammatory changes potentially contributing to autonomic dysregulation, altered joint innervation patterns and chronic nociceptive signaling could also lead to autonomic dysfunction and shifts in the HPA-axis. Next, we briefly discuss how OA pain generation overlaps with the autonomic nervous system and potentially leads to shifts in autonomic responses. Please note this discussion of neuronal plasticity related to OA pain is brief and focused on autonomic overlap; more in-depth reviews of the neurobiology of OA pain are available [44–48].

OA pain can be generated via altered responses to stimuli that are both normally non-painful (i.e., allodynia) and normally painful (i.e., hyperalgesia). In a healthy synovial joint, a noxious stimulus will activate pain-sensing nociceptors from the capsule, ligaments, menisci, periosteum, and subchondral bone [49–54]. However, with OA pathogenesis, there is an increase in sensitivity of existing joint nociceptors, likely caused by inflammation in the joint [55, 56]. Increased signaling from nociceptive neurons pass through the spinal cord and reach the nucleus tractus solitarii (NTS) region of the brain stem, where signals are integrated and sent to pain centers like the periaqueductal gray (Fig. 1, black line). Here, the NTS and periaqueductal gray also play key roles in regulating autonomic functions; thus, repeated signals from the OA joint could cause changes in sympathetic and parasympathetic drive via the NTS and periaqueductal gray [57]. This highlights the potential of autonomic cross talk related to nociceptive signaling from degenerating joints.

Beyond the articular joint, decreased action potential thresholds have been found in the dorsal horn of the spinal cord of OA animal models, whereby a lower threshold increases the propensity of spinal afferent neuronal firing [58]. Additionally, evidence of neuropathic pain has also been observed in both OA animal models [59] and OA patients [60]. All these mechanisms may increase pain-signaling from the OA joint to the NTS and periaqueductal gray, with potential concomitant effects on autonomic functions due to the overlap of these pain centers with autonomic regulation. Structural and functional relationships between autonomic and pain-related brain areas are modulated by chronic pain. These associations, discussed below, apply generally to chronic pain states, but can inform future studies specific to OA pain signals.

Many regions of the central autonomic network, which include the brain and spinal cord regions that control the autonomic nervous system, overlap with regions involved in the pain processing centers of the brain, commonly referred to as the pain matrix. For example, the dorsal anterior cingulate cortex and the periaqueductal gray both play a role in autonomic control and in pain perception [61, 62]. One preliminary neuroimaging study reported a three-way connection between the autonomic nervous system, cortical regions involved in pain, and self-reported pain measures, partly demonstrating a connection between autonomics and pain [63•]. Additionally, an fMRI study by Stroman et. al. demonstrated functional connectivity between the periaqueductal gray, hypothalamus, and several brain areas associated with autonomic regulation (i.e., parabrachial nucleus and NTS). This functional connection with descending nociceptive modulation may be related to autonomic

reactivity or homeostatic autonomic regulation [64•]. Furthermore, we have shown patients with chronic pain display blunted sympathetic reactivity during simple and complex walking tasks, which is associated with changes in central autonomic network grey matter volumes [65]. The results of this preliminary study may suggest chronic pain impacts typical autonomic responses required for performance tasks, like simple and complex walking, potentially through changes to brain structure. Further research involving large-scale chronic pain populations, including OA patients, is needed to investigate structural and functional overlaps between the central autonomic network and the central pain matrix.

Beyond physiological causes of painful signals, pain is ultimately the interpretation of these signals as painful within the brain. Here, the biopsychosocial model of pain helps explain how environmental stressors, state of mind, and cultural factors can all influence the perception of pain [66]. Heterogeneity of the human pain experience can be largely attributed to the complex integration of these influences, and thus, these factors should be considered when studying chronic pain diseases like OA. The biological processes referred to by this model include the biological processes, including nociceptive, endocrine, immunological, and genetic influences, that occur in the experience of pain. Advanced techniques in preclinical research, such as electrophysiological recordings, allow us to expand our mechanistic understanding of the underlying neurobiological mechanisms of chronic OA pain. The “psycho” of biopsychosocial refers to both emotional and cognitive components of the pain experience we are currently able to explore in both clinical and preclinical models through structural, functional, and biochemical neuroimaging techniques. Since these assessments are relatively comparable across species, preclinical research can help close gaps between painful signaling and pathophysiologic changes related to OA, while clinical research can allow us to relate the subjective pain experience to these interactions measured in the brain. Thus, parallels can be drawn between the human experience of pain, neuroimaging in humans and animals, and mechanistic studies in animal models to create a translational continuum in OA research, as discussed in the next section.

Bridging the Preclinical to Clinical Translational Divide to Close Gaps in Our Understanding of Autonomic Dysfunction in OA

Preclinical models of chronic pain diseases, such as OA, are the engines of therapeutic discovery and allow for well-controlled mechanistic studies. In general, animal models can control for disease heterogeneity and environmental factors, allowing the study of specific contributions from different pathophysiologic features of OA. For example, transgenic models have been utilized to study influences of specific genes on OA pathophysiology. Powerful investigative techniques, like live nerve recordings and histological evaluations of pathologic factors, are commonly applied in animal studies in ways that are simply not possible in humans. Additionally, animal models allow for first pass testing of emerging therapeutic strategies. Clearly, the advantage of utilizing animal models is the ability to precisely determine the biological mechanisms underlying disease pathophysiology to identify and test potential therapeutic targets.

While animal models can be useful, cautions must be taken when applying findings to the human disease. First, OA models are limited to surgical, injury, and chemical models

that cannot fully recapitulate human pathology. For instance, the monoiodoacetate (MIA) injection model of OA induces cartilage damage, alters joint nociception, and causes neuropathy, but this model has only a 4% transcriptional overlap between cartilage collected from the MIA model relative to human OA cartilage [67]. Additionally, often overlooked socialization variables, including housing, environmental enrichment, and habituation to testing apparatuses, can all influence stress responses and therefore outcomes of behavioral assessments. Finally, animal strain should be carefully selected and evaluated. As mentioned previously, Lewis rats have a hyporesponsive HPA-axis that may influence inflammatory measures and stress responses [68, 69]. Lewis rats are commonly used in OA research and are recommended by the OARSI histopathology initiative [70]. Conversely, Sprague-Dawley rats have a more intact HPA axis and exhibit larger cartilage cysts compared to Lewis rats in the medial meniscus transection model of OA [70]. It is possible larger cartilage cysts are due to more intact HPA-axis and the associated increase in endogenous glucocorticoid levels. In fact, deletion of the chondrocyte glucocorticoid receptor decreases cartilage degradation in the destabilization of medial meniscus model of OA [71]. Here, the limitations of animal research do not necessarily preclude successful studies related to autonomic functions in OA, but rather, this should encourage researchers to carefully control their experiments and interpret results in the context of these systemic factors.

While preclinical studies may allow us to probe specific pathologic mechanisms in a controlled manner, human studies provide the ability to explore the influences of psychosocial variables, such as emotional state, coping, social support, education, and income, and the intersectionality of these factors in the context of chronic pain. Importantly, unlike rodents, people can self-report perceived pain experience and psychological variables. Because psychological variables are important in the generation of chronic pain and autonomic function, collecting these self-report measures will allow us to explore the underlying associations and create individualized therapeutic strategies more readily. Moreover, with biological techniques that bridge clinical and preclinical research, such as some behavioral assessments, some measurements in tissue biopsies, and neuroimaging, we can begin to draw parallels between human clinical studies and animal pathophysiologic studies, even if psychosocial factors from human studies cannot be fully replicated in preclinical studies. However, by understanding the biological shifts caused by psychosocial variables in humans, we can better inform our biological targets in preclinical studies of new therapeutic strategies.

Again, this translational continuum framework can be readily applied to study the autonomic nervous system. First, autonomic mechanisms are generally conserved between humans and rodents [72, 73]. Additionally, many techniques can be applied in a parallel fashion in both rodents and humans. For example, heart rate variability, a measure of autonomic function, can be measured via radiotelemetry in rodents, while simple ECG monitors can be applied to humans. Neuroimaging techniques can also be applied in both humans and rodents to study overlaps of the central autonomic network and pain matrix in the brain. Thus, the animal model can help to fill some mechanistic gaps, while clinical research provides more robust assessment of the perceived pain experience. This translational continuum framework could be readily applied to studies testing the hypothesis of underlying autonomic dysfunction,

such as the relationship between OA and common co-morbidities with known autonomic dysfunction (i.e. hypertension, diabetes, etc.).

Non-Pharmacologic Pain Interventions via Regulation of the Autonomic Nervous System

Some non-pharmacological therapies for OA pain may partly function through autonomic mechanisms, including bioelectric medicine approaches, physical rehabilitation, and mind-body interventions. If the autonomic nervous system is dysregulated, targeting it could rebalance stress response systems and associated systemic inflammation. As discussed above, there are known overlaps between chronic pain, inflammation, and autonomic function; thus, therapies that modulate autonomic function have the potential to alleviate pain and inflammation associated with OA.

One method of co-opting the autonomic nervous system is through electrical stimulation of the vagus nerve. As discussed previously, the vagus is the main nerve of the parasympathetic nervous system and is an important regulator of inflammatory homeostasis. Bioelectric stimulation of the vagus has been proposed to have potent anti-inflammatory effects [74]. In fact, several preclinical and clinical studies have evaluated these actions in rheumatic joint diseases. For example, vagal nerve stimulation decreased joint-level inflammation in rodent models of collagen-induced inflammatory arthritis by lowering joint neutrophil levels [28, 75]. Clinically, vagal nerve stimulation has lowered inflammation and clinical scores in RA patients [76]. To our knowledge, only one study has clinically evaluated vagal nerve stimulation in OA; here, auricular vagal nerve stimulation decreased median measures of hand pain, joint tenderness, and swelling in patients with erosive hand OA [77•]. Thus, there is some evidence of vagus nerve stimulation as a therapeutic strategy for joint inflammation; however, further study is clearly needed to evaluate the potential to modulate OA pain and disease.

Exercise is well known to have an analgesic effect in chronic pain populations. Exercise also has known, strong effects on autonomic functions, including regulation of arterial baroreflex and cardiovascular functions [78]. In OA patients, moderate exercise reduces weight and strengthens extra-articular muscles, which can improve joint biomechanics by increasing stability and reducing knee loads[79]. However, beyond the joint, exercise modifies inflammation throughout the body and improves the neuro-immune response to stress. Moreover, within the biopsychosocial model, exercise reduces stress, anxiety, and fear avoidance [80]. Thus, under the lens of both autonomic feedback and the biopsychosocial model, exercise can cause shifts in the autonomic nervous system that may counteract pathologic and psychologic modulators of OA pain. When the exercise-induced autonomic feedback is impaired, such as in patients with myalgic encephalomyelitis or chronic fatigue syndrome, exercise-induced analgesia is lessened [81]. Thus, exercise-induced analgesia in chronic pain states may interact with exercise's regulation of autonomic nervous system. Relationships between exercise-induced analgesia and autonomic function, as well as the possible dysregulation of these interactions, is worth further exploration in the context of OA and the OA pain experience.

Finally, mind-body interventions are of growing interest for management of chronic pain [82, 83]. Here, autonomic balance is hypothesized to be an underlying mechanism

for interventions, such as mindfulness meditation, breathing exercises, spiritual therapy, imagery, tai chi, yoga, acupuncture, and aroma therapy, among others [84]. With dysregulation of the autonomic nervous system, the body's ability to adapt to common life events, such as pain control, is diminished. In fact, ongoing research is examining mindfulness and other mind-body practices in relation to OA pathophysiology and symptomology. For example, mindfulness practices may moderate the influence of pain on stress responses in OA patients [85]. Additionally, the combination of a bioelectric medicine approach (e.g., transcranial direct current stimulation) and mindfulness-based meditation improved WOMAC scores, increased pressure pain thresholds, and improved conditioned pain modulation responses [86]. There is ongoing work in this area through the collaborative pain relief for osteoarthritis through combined treatment (PROACT) clinical trial [87]. Possibly, mindfulness practices may reduce stress and minimize cortisol secretion to rebalance autonomics, thereby lowering pain perception [88]. Combined, non-pharmacological interventions that target the autonomic nervous system are becoming increasingly supported, and a better understanding of the interactions between OA and autonomic dysregulation could help further refine these interventions in the future. Moreover, a better understanding of the physiologic consequences of autonomic dysregulation in OA could lead to new management plans that combine pharmacologic and non-pharmacologic OA treatments that treat the joint and the whole patient, thereby providing relief from pain and disability associated with OA.

Conclusions

The autonomic nervous system may provide a framework for exploring some of the 'whole-body' interactions underlying neurobiological mechanisms of OA. For example, chronic activation of joint nociceptors and autonomic stress response factors may interact bi-directionally to perpetuate OA pain and inflammation. From this, dysregulation of the autonomic nervous system could lead to whole-body changes, including modulation of the functional interactions between the central autonomic network and pain matrix in the brain. Additionally, as autonomic dysregulation is present in other diseases, including common comorbidities of OA (i.e., hypertension and diabetes), the autonomic nervous system may contribute to the comorbid presentation of such diseases. The translational continuum of preclinical to clinical research provides an opportunity to robustly study the interactions between the autonomic nervous system and the generation of OA pain and disability. For example, within the biopsychosocial model of chronic pain, animal models can allow us to mechanistically explore the biological and physiological changes occurring within and beyond the joint. Human studies will also allow us to confirm higher level pathophysiological changes and study psycho-social effects, like stress, depression, anxiety, catastrophizing, resilience. From this, both pharmacologic and non-pharmacological treatments for OA pain can be tested and potentially combined in a meaningful fashion. With this, the autonomic nervous system provides a unique opportunity for combinatorial pain interventions, where pharmacological interventions to reduce nociception could be done simultaneously with non-pharmacological approaches that reduce the perceptive experience of pain. Illumination of the interactions between autonomic dysfunction and

OA through various preclinical and clinical studies could lead to novel approaches to management of OA pain.

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References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. WHO Department of Health Statistics and Information Systems (2013) World Health Organization methods and data sources for global burden of disease estimates 2000–2011. Geneva
2. Loeser RF, Goldring SR, Scanzello CR, Goldring MB (2012) Osteoarthritis: A disease of the joint as an organ. Arthritis and Rheumatism 64:1697–1707 [PubMed: 22392533]
3. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, Campbell CM, Haythornthwaite JA, Edwards RR, Smith MT (2013) Discordance between pain and radiographic severity in knee osteoarthritis: Findings from quantitative sensory testing of central sensitization. Arthritis & Rheumatism 65:363–372 [PubMed: 22961435]
4. Bannuru RR, Osani MC, Vaysbrot EE, et al. (2019) OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis and Cartilage 27:1578–1589 [PubMed: 31278997]
5. Pre-Competitive Consortium for Osteoarthritis of the Osteoarthritis Research International (2016) Osteoarthritis: A Serious Disease, Submitted to the U.S. Food and Drug Administration.
6. Lanza FL, Chan FKL, Quigley EMM, et al. (2009) Guidelines for prevention of NSAID-related ulcer complications. American Journal of Gastroenterology 104:728–738 [PubMed: 19240698]
7. Liu G, Yan YP, Zheng XX, Xu YL, Lu J, Hui RT, Huang XH (2014) Meta-analysis of nonsteroidal anti-inflammatory drug use and risk of atrial fibrillation. American Journal of Cardiology 114:1523–1529 [PubMed: 25260945]
8. Hsu CC, Wang H, Hsu YH, Chuang SY, Huang YW, Chang YK, Liu JS, Hsiung CA, Tsai HJ (2015) Use of Nonsteroidal Anti-Inflammatory Drugs and Risk of Chronic Kidney Disease in Subjects with Hypertension: Nationwide Longitudinal Cohort Study. Hypertension 66:524–533 [PubMed: 26169048]
9. Andriacchi TP, Griffin TM, Loeser RF, Chu CR, Roos EM, Hawker GA, Erhart-Hledik JC, Fischer AG (2020) Bridging Disciplines as a pathway to Finding New Solutions for Osteoarthritis a collaborative program presented at the 2019 Orthopaedic Research Society and the Osteoarthritis Research Society International. Osteoarthritis and Cartilage Open 2:100026
10••. Courties A, Sellam J, Berenbaum F (2017) Role of the autonomic nervous system in osteoarthritis. Best Practice & Research Clinical Rheumatology 31:661–675 [PubMed: 30509412] Provides framework for the contributions of the autonomic nervous system to osteoarthritis pathophysiology
11. Berenbaum F, Meng QJ (2016) The brain-joint axis in osteoarthritis: Nerves, circadian clocks and beyond. Nature Reviews Rheumatology 12:508–516 [PubMed: 27305851]
12. Pavlov VA, Tracey KJ (2012) The vagus nerve and the inflammatory reflex - Linking immunity and metabolism. Nature Reviews Endocrinology 8:743–754
13. Boscan P, Kasparov S, Paton JFR (2002) Somatic nociception activates NK1 receptors in the nucleus tractus solitarii to attenuate the baroreceptor cardiac reflex. European Journal of Neuroscience 16:907–920 [PubMed: 12372027]

14. Pickering AE, Boscan P, Paton JFR (2003) Nociception attenuates parasympathetic but not sympathetic baroreflex via NK1 receptors in the rat nucleus tractus solitarii. Journal of Physiology 551:589–599 [PubMed: 12813142]
15. Rotenberg S, McGrath JJ (2016) Inter-relation between autonomic and HPA axis activity in children and adolescents. Biological Psychology 117:16–25 [PubMed: 26835595]
16. Villafañe JH et al. , "Exploring the relationship between chronic pain and cortisol levels in subjects with osteoarthritis: results from a systematic review of the literature," Osteoarthr. Cartil, vol. 28, no. 5, pp. 572–580, May 2020.
17. Yang X, Qi Y, Avercenc-Leger L, Vincourt JB, Hupont S, Huselstein C, Wang H, Chen L, Magdalou J (2017) Effect of nicotine on the proliferation and chondrogenic differentiation of the human Wharton's jelly mesenchymal stem cells. In: Bio-Medical Materials and Engineering. Biomed Mater Eng, pp S217–S228 [PubMed: 28372298]
18. Kawakita A, Sato K, Makino H, Ikegami H, Takayama S, Toyama Y, Umezawa A (2008) Nicotine acts on growth plate chondrocytes to delay skeletal growth through the α7 neuronal nicotinic acetylcholine receptor. PLoS ONE 3:e3945 [PubMed: 19079602]
19. Liu Y, Wu D, Song F, Zhu C, Hui Y, Zhu Q, Wu J, Fan W, Hu J (2015) Activation of α7 nicotinic acetylcholine receptors prevents monosodium iodoacetate-induced osteoarthritis in rats. Cellular Physiology and Biochemistry 35:627–638 [PubMed: 25613062]
20. Fujii T, Mashimo M, Moriwaki Y, Misawa H, Ono S, Horiguchi K, Kawashima K (2017) Expression and function of the cholinergic system in immune cells. Frontiers in Immunology. 10.3389/fimmu.2017.01085
21. Chisari E, Wouthuyzen-Bakker M, Friedrich AW, and Parvizi J, "The relation between the gut microbiome and osteoarthritis: A systematic review of literature," PLoS One, vol. 16, no. 12, p. e0261353, Dec. 2021. [PubMed: 34914764]
22. Minerbi A et al. , "Altered microbiome composition in individuals with fibromyalgia," Pain, vol. 160, no. 11, pp. 2589–2602, Nov. 2019. [PubMed: 31219947]
23. Martins DF et al. , "The role of the vagus nerve in fibromyalgia syndrome," Neurosci. Biobehav. Rev, vol. 131, pp. 1136–1149, Dec. 2021. [PubMed: 34710514]
24. Gupta VK et al. , "Gut microbial determinants of clinically important improvement in patients with rheumatoid arthritis," Genome Med, vol. 13, no. 1, pp. 1–20, Dec. 2021. [PubMed: 33397400]
25. Ingegnoli F, Buoli M, Antonucci F, Coletto LA, Esposito CM, and Caporali R, "The Link Between Autonomic Nervous System and Rheumatoid Arthritis: From Bench to Bedside," Front. Med, vol. 7, p. 859, Dec. 2020.
26. Dekker Nitert M, Mousa A, Barrett HL, Naderpoor N, and de Courten B, "Altered Gut Microbiota Composition Is Associated With Back Pain in Overweight and Obese Individuals," Front. Endocrinol. (Lausanne), vol. 11, p. 605, Sep. 2020. [PubMed: 32982987]
27. El-Badawy MA and El Mikkawy DME, "Sympathetic dysfunction in patients with chronic low back pain and failed back surgery syndrome," Clin. J. Pain, vol. 32, no. 3, pp. 226–231, 2016. [PubMed: 25968450]
28. Bassi GS, Dias DPM, Franchin M, et al. (2017) Modulation of experimental arthritis by vagal sensory and central brain stimulation. Brain, Behavior, and Immunity 64:330–343 [PubMed: 28392428]
29. Konttinen YT, Sillat T, Barreto G, Ainola M, Nordström DCE (2012) Osteoarthritis as an autoinflammatory disease caused by chondrocyte-mediated inflammatory responses. Arthritis and Rheumatism 64:613–616 [PubMed: 22130805]
30. Lorenz J, Schäfer N, Bauer R, Jenei-Lanzl Z, Springorum RH, Grässel S (2016) Norepinephrine modulates osteoarthritic chondrocyte metabolism and inflammatory responses. Osteoarthritis and Cartilage 24:325–334 [PubMed: 26327449]
31. Courties A, Do A, Leite S, et al. (2020) The Role of the Non-neuronal Cholinergic System in Inflammation and Degradation Processes in Osteoarthritis. Arthritis & Rheumatology 72:2072–2082 [PubMed: 32638534]
32. Bock K, Plaass C, Coger V, Peck C-T, Reimers K, Stukenborg-Colsman C, Claassen L (2016) What is the effect of nicotinic acetylcholine receptor stimulation on osteoarthritis in a rodent animal model? SAGE Open Medicine 4:205031211663752

33. Courties A, Do A, Leite S, et al. (2019) Activating the cholinergic system a novel opportunity for treating osteoarthritis. Osteoarthritis and Cartilage 27:S38
34. Teng P, Liu Y, Dai Y, Zhang H, Liu W-T, Hu J (2019) Nicotine Attenuates Osteoarthritis Pain and Matrix Metalloproteinase-9 Expression via the α7 Nicotinic Acetylcholine Receptor. The Journal of Immunology 203:485–492 [PubMed: 31152077]
35. Louati K, Berenbaum F (2015) Fatigue in chronic inflammation - a link to pain pathways. Arthritis Research and Therapy. 10.1186/s13075-015-0784-1
36. Farzi A, Fröhlich EE, Holzer P (2018) Gut Microbiota and the Neuroendocrine System. Neurotherapeutics 15:5–22 [PubMed: 29380303]
37. Franciosi S, Perry FKG, Roston TM, Armstrong KR, Claydon VE, Sanatani S (2017) The role of the autonomic nervous system in arrhythmias and sudden cardiac death. Autonomic Neuroscience: Basic and Clinical 205:1–11 [PubMed: 28392310]
38. Olofsson PS, Rosas-Ballina M, Levine YA, Tracey KJ (2012) Rethinking inflammation: Neural circuits in the regulation of immunity. Immunological Reviews 248:188–204 [PubMed: 22725962]
39. Provan SA, Olstad DS, Solberg EE, Smedslund G, Dagfinrud H (2018) Evidence of reduced parasympathetic autonomic regulation in inflammatory joint disease: A meta-analyses study. Seminars in Arthritis and Rheumatism 48:134–140 [PubMed: 29291895]
40. Adlan AM, Veldhuijzen van Zanten JJCS, Lip GYH, Paton JFR, Kitas GD, Fisher JP (2017) Cardiovascular autonomic regulation, inflammation and pain in rheumatoid arthritis. Autonomic Neuroscience: Basic and Clinical 208:137–145 [PubMed: 28927867]
41. van Maanen MA, Stoof SP, LaRosa GJ, Vervoordeldonk MJ, Tak PP (2010) Role of the cholinergic nervous system in rheumatoid arthritis: Aggravation of arthritis in nicotinic acetylcholine receptor α7 subunit gene knockout mice. Annals of the Rheumatic Diseases 69:1717–1723 [PubMed: 20511609]
42. Sternberg EM, Hill JM, Chrousos GP, Kamilaris T, Listwak SJ, Gold PW, Wilder RL (1989) Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats. Proceedings of the National Academy of Sciences of the United States of America 86:2374–2378 [PubMed: 2538840]
43. Yeater TD, Zubcevic J, Allen KD Measures of Cardiovascular Function Suggest Autonomic Nervous System Dysregulation after Surgical Induction of Joint Injury in the Male Lewis Rat. Osteoarthritis and Cartilage (In Press):
44. Fu K, Robbins SR, McDougall JJ (2018) Osteoarthritis: The genesis of pain. Rheumatology (United Kingdom) 57:iv43–iv50
45. McDougall J (2006) Arthritis and pain: Neurogenic origin of joint pain. Arthritis Research & Therapy. 10.1186/ar2069
46. Malfait AM, Miller RJ (2016) Emerging Targets for the Management of Osteoarthritis Pain. Current Osteoporosis Reports 14:260–268 [PubMed: 27730452]
47. Eitner A, Hofmann GO, Schaible H-G, Kress M, Cunha TM (2017) Mechanisms of Osteoarthritic Pain. Studies in Humans and Experimental Models. 10:1–22
48. Schaible HG (2018) Osteoarthritis pain. Recent advances and controversies. Current Opinion in Supportive and Palliative Care 12:148–153 [PubMed: 29438127]
49. McDougall JJ, Bray RC, Sharkey KA (1997) Morphological and immunohistochemical examination of nerves in normal and injured collateral ligaments of rat, rabbit, and human knee joints. Anatomical Record 248:29–39 [PubMed: 9143665]
50. Mach DB, Rogers SD, Sabino MC, et al. (2002) Origins of skeletal pain: Sensory and sympathetic innervation of the mouse femur. Neuroscience 113:155–166 [PubMed: 12123694]
51. Serre CM, Farlay D, Delmas PD, Chenu C (1999) Evidence for a dense and intimate innervation of the bone tissue, including glutamate-containing fibers. Bone 25:623–629 [PubMed: 10593406]
52. O'Connor BL (1984) The mechanoreceptor innervation of the posterior attachments of the lateral meniscus of the dog knee joint. Journal of Anatomy 138:15–26 [PubMed: 6706833]
53. Freeman MAR, Wyke B (1967) The innervation of the knee joint. An anatomical and histological study in the cat. Journal of Anatomy 101:505 [PubMed: 6051731]
54. Marinozzi G, Ferrante F, Goudio E, Ricci A, Amenta F (1991) Intrinsic innervation of the rat knee joint articular capsule and ligaments. Acta Anat (Basel) 141:8–14 [PubMed: 1950424]

55. Schuelert N, McDougall JJ (2009) Grading of monosodium iodoacetate-induced osteoarthritis reveals a concentration-dependent sensitization of nociceptors in the knee joint of the rat. Neuroscience Letters 465:184–188 [PubMed: 19716399]
56. O'Brien MS, McDougall JJ (2020) Neurophysiological assessment of joint nociceptors in the rat medial meniscus transection model of post-traumatic osteoarthritis. Osteoarthritis and Cartilage 28:1255–1264 [PubMed: 32416224]
57. Cortelli P, Giannini G, Favoni V, Cevoli S, Pierangeli G (2013) Nociception and autonomic nervous system. Neurol Sci 34:S41–S46 [PubMed: 23695044]
58. Woolf CJ (2011) Central sensitization: Implications for the diagnosis and treatment of pain. Pain. 10.1016/j.pain.2010.09.030
59. Thakur M, Rahman W, Hobbs C, Dickenson AH, Bennett DLH (2012) Characterisation of a peripheral neuropathic component of the rat monoiodoacetate model of osteoarthritis. PLoS ONE. 10.1371/journal.pone.0033730
60. Terry EL, Booker SQ, Cardoso JS, et al. (2020) Neuropathic-like pain symptoms in a community-dwelling sample with or at risk for knee osteoarthritis. Pain Medicine (United States) 21:125–137
61. Leone M, Proietti Cecchini A, Mea E, Tullo V, Curone M, Bussone G (2006) Neuroimaging and pain: A window on the autonomic nervous system. Neurological Sciences 27:s134–s137 [PubMed: 16688617]
62. Heinricher MM, Fields HL (2013) Central nervous system mechanisms of pain modulation. Wall and Melzack's textbook of pain 6:129–142
63•. Hohenschurz-Schmidt DJ, Calcagnini G, Dipasquale O, et al. (2020) Linking Pain Sensation to the Autonomic Nervous System: The Role of the Anterior Cingulate and Periaqueductal Gray Resting-State Networks. Frontiers in Neuroscience 14:147 [PubMed: 33041747] Evidence for centrally mediated functional connections between pain and autonomics
64•. Stroman PW, Ioachim G, Powers JM, Staud R, Pukall C (2018) Pain processing in the human brainstem and spinal cord before, during, and after the application of noxious heat stimuli. Pain 159:2012–2020 [PubMed: 29905656] Evidence for centrally mediated functional connections between pain and autonomics
65. Yeater TD, Clark DJ, Hoyos L, Valdes-Hernandez PA, Peraza JA, Allen KD, Cruz-Almeida Y (2021) Chronic Pain is Associated With Reduced Sympathetic Nervous System Reactivity During Simple and Complex Walking Tasks: Potential Cerebral Mechanisms. Chronic Stress. 10.1177/24705470211030273
66. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC (2007) The Biopsychosocial Approach to Chronic Pain: Scientific Advances and Future Directions. Psychological Bulletin 133:581–624 [PubMed: 17592957]
67. Barve RA, Minnerly JC, Weiss DJ, Meyer DM, Aguiar DJ, Sullivan PM, Weinrich SL, Head RD (2007) Transcriptional profiling and pathway analysis of monosodium iodoacetate-induced experimental osteoarthritis in rats: relevance to human disease. Osteoarthritis and Cartilage 15:1190–1198 [PubMed: 17500014]
68. Aksentijevich S, Whitfield HJ, Scott Young W, Wilder RL, Chrousos GP, Gold PW, Sternberg EM (1992) Arthritis-susceptible Lewis rats fail to emerge from the stress hyporesponsive period. Developmental Brain Research 65:115–118 [PubMed: 1551226]
69. Chaouloff F, Kulikov A, Sarrieau A, Castanon N, Mormède P (1995) Male Fischer 344 and Lewis rats display differences in locomotor reactivity, but not in anxiety-related behaviours: relationship with the hippocampal serotonergic system. Brain Research 693:169–178 [PubMed: 8653405]
70. Gerwin N, Bendele AM, Glasson S, Carlson CS (2010) The OARSI histopathology initiative - recommendations for histological assessments of osteoarthritis in the rat. Osteoarthritis and Cartilage. 10.1016/j.joca.2010.05.030
71. Macfarlane E, Seibel MJ, and Zhou H, "Arthritis and the role of endogenous glucocorticoids," Bone Res, vol. 8, no. 1, Dec. 2020.
72. Kenwood MM, Kalin NH, Barbas H (2022) The prefrontal cortex, pathological anxiety, and anxiety disorders. Neuropsychopharmacology 47:260–275 [PubMed: 34400783]
73. Young HM, Cane KN, Anderson CR (2011) Development of the autonomic nervous system: A comparative view. Autonomic Neuroscience: Basic and Clinical 165:10–27 [PubMed: 20346736]

74. Koopman FA, Chavan SS, Miljko S, et al. (2016) Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in Rheumatoid arthritis. Proceedings of the National Academy of Sciences of the United States of America 113:8284–8289 [PubMed: 27382171]

75. Levine YA, Koopman FA, Faltys M, Caravaca A, Bendele A, Zitnik R, Vervoordeldonk MJ, Tak PP (2014) Neurostimulation of the cholinergic anti-inflammatory pathway ameliorates disease in rat collagen-induced arthritis. PLoS ONE. 10.1371/journal.pone.0104530

76. Marsal S, Corominas H, Lopez Lasanta M, et al. (2020) SAT0133 PILOT CLINICAL STUDY OF A NON-INVASIVE AURICULAR VAGUS NERVE STIMULATION DEVICE IN PATIENTS WITH RHEUMATOID ARTHRITIS. Annals of the Rheumatic Diseases. 10.1136/annrheumdis-2020-eular.3315

77•. Courties A, Deprouw C, Maheu E, Gibert E, Gottenberg J-E, Champey J, Rousseau A, Berenbaum F, Sellam J (2020) Transcutaneous auricular stimulation of the vagus nerve for erosive hand osteoarthritis an open label pilot study. Osteoarthritis and Cartilage. 10.1016/j.joca.2020.02.562 First study on vagal nerve stimulation in osteoarthritis

78. Fu Q, Levine BD (2013) Exercise and the autonomic nervous system. In: Handbook of Clinical Neurology. Elsevier, pp 147–160

79. Thorstensson CA, Henriksson M, von Porat A, Sjödahl C, Roos EM (2007) The effect of eight weeks of exercise on knee adduction moment in early knee osteoarthritis - a pilot study. Osteoarthritis and Cartilage 15:1163–1170 [PubMed: 17466541]

80. Hunt MA, Birmingham TB, Skarakis-Doyle E, Vandervoort AA (2008) Towards a biopsychosocial framework of osteoarthritis of the knee. Disability and Rehabilitation 30:54–61 [PubMed: 17852218]

81. van Oosterwijck J, Marusic U, de Wandele I, Paul L, Meeus M, Moorkens G, Lambrecht L, Danneels L, Nijs J (2017) The role of autonomic function in exerciseinduced endogenous analgesia: A case-control study in myalgic encephalomyelitis/chronic fatigue syndrome and healthy people. Pain Physician 20:E389–E399 [PubMed: 28339438]

82. Goyal M, Singh S, Sibinga EMS, et al. (2014) Meditation programs for psychological stress and well-being: A systematic review and meta-analysis. JAMA Internal Medicine 174:357–368 [PubMed: 24395196]

83. Stanos S (2012) Focused review of interdisciplinary pain rehabilitation programs for chronic pain management. Current Pain and Headache Reports 16:147–152 [PubMed: 22427179]

84. Tang YY, Hölzel BK, Posner MI (2015) The neuroscience of mindfulness meditation. Nature Reviews Neuroscience 16:213–225 [PubMed: 25783612]

85. Lee A, Harvey W, Price L, Morgan L, Morgan N, Wang C (2017) Mindfulness is associated with psychological health and moderates pain in knee osteoarthritis. Osteoarthritis and Cartilage 25:824–831 [PubMed: 27349461]

86. Ahn H, Zhong C, Miao H, Chaoul A, Park L, Yen I, Vila M, Sorkpor S, Abdi S (2019) Efficacy of combining home-based transcranial direct current stimulation with mindfulness-based meditation for pain in older adults with knee osteoarthritis: A randomized controlled pilot study. Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia 70:140–145 [PubMed: 31421990]

87. Fillingim R, Woods A, Ahn H, et al. (2020) Pain relief for osteoarthritis through combined treatment (PROACT): Protocol for a randomized controlled trial of mindfulness meditation combined with transcranial direct current stimulation in non-Hispanic black and white adults with knee osteoarthritis. Contemporary clinical trials. 10.1016/J.CCT.2020.106159

88. Hannibal KE, Bishop MD (2014) Chronic stress, cortisol dysfunction, and pain: A psychoneuroendocrine rationale for stress management in pain rehabilitation. Physical Therapy 94:1816–1825 [PubMed: 25035267]

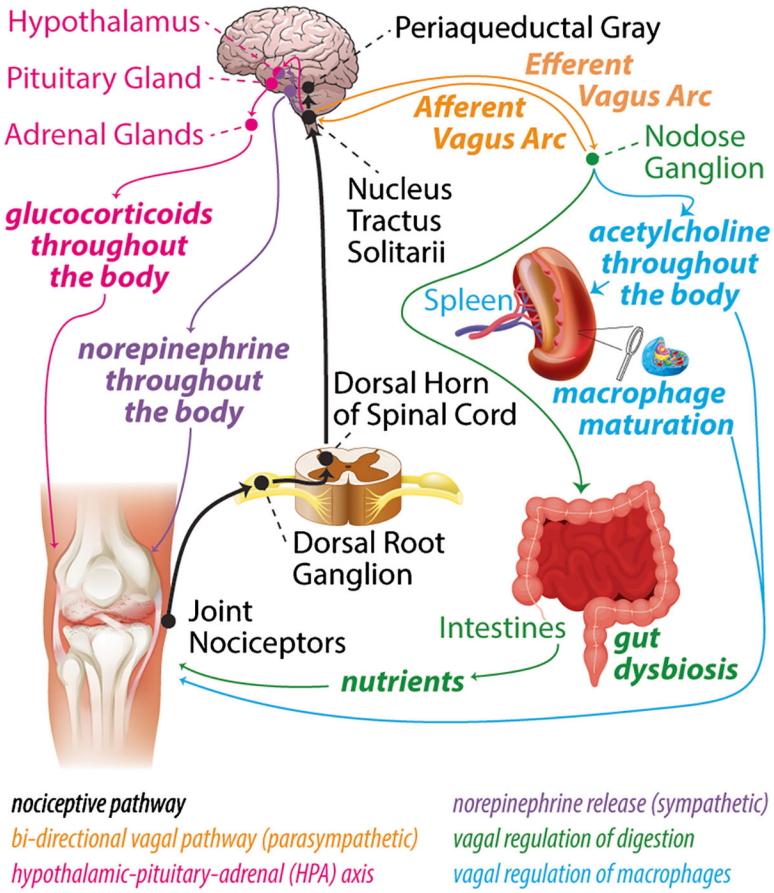

Figure 1:
Crosstalk between the brain, joint, and autonomic nervous systems.