

Marquette University

e-Publications@Marquette

Physical Therapy Faculty Research and
Publications

Physical Therapy, Department of

9-2018

Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation

Kathleen A. Sluka

Laura Frey-Law

Marie K. Hoeger Bement

Follow this and additional works at: https://epublications.marquette.edu/phys_therapy_fac

 Part of the [Physical Therapy Commons](#)

Marquette University

e-Publications@Marquette

Physical Therapy Faculty Research and Publications/College of Health Sciences

This paper is NOT THE PUBLISHED VERSION; but the author's final, peer-reviewed manuscript. The published version may be accessed by following the link in the citation below.

Pain, Vol. 159 (September 2018): S91-S97. [DOI](#). This article is © Wolters Kluwer and permission has been granted for this version to appear in [e-Publications@Marquette](#). Wolters Kluwer does not grant permission for this article to be further copied/distributed or hosted elsewhere without the express permission from Wolters Kluwer.

Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation

Kathleen A. Sluka

Department of Physical Therapy and Rehabilitation Science, The University of Iowa, Iowa City, IA
Neuroscience Institute, The University of Iowa, Iowa City, IA,
Pain Research Program, The University of Iowa, Iowa City, IA

Laura Frey-Law

Department of Physical Therapy and Rehabilitation Science, The University of Iowa, Iowa City, IA

Marie Hoeger Bement

Department of Physical Therapy, Marquette University, Milwaukee, WI

1. Introduction

Physical inactivity or a sedentary lifestyle is a significant health concern worldwide. The Centers for Disease Control (CDC) recommends 150 minutes per week of moderate to vigorous activity for health benefits.¹³ Worldwide, the great majority of the population does not meet these physical activity guidelines. Furthermore, physical inactivity is a recognized risk factor for many conditions including cardiovascular disease, diabetes, cancer, dementia, and depression⁶⁹ (Fig. 1). In fact, this has been

referred to as the "diseasome of physical inactivity."⁶⁹ Physical inactivity is also a risk factor for the development of pain.^{50,51,89} The HUNT study performed a population-based analysis of 4219 subjects and showed that those with moderate levels' physical activity report less musculoskeletal pain.^{50,51} Similarly, higher leisure-time physical activity is associated with a lower risk of chronic pelvic pain in men,⁸⁹ and those with a greater number of years of leisure physical activity decreased the risk of low back pain (LBP) during pregnancy.⁶³ Thus, physical inactivity may be a risk factor for the development of chronic pain, whereas physical activity reduces this risk.



Figure 1. Diagram representing the diseasome of physical inactivity. Physical inactivity is a risk factor for the development of a number of diseases including pain. Modified from Ref. 69, with permission from the publisher, John Wiley & Sons, Inc.

Regular physical activity can be achieved through regular lifestyle activity or by structured exercise. In chronic pain, prescribed exercise is an effective treatment for most pain conditions, and use of exercise and physical therapy has long been recognized for its effectiveness in reducing disability and health care costs.^{40,42,84} Despite this, an acute bout of exercise can exacerbate pain, in those with chronic pain. As an example, we have shown that an upper-body fatiguing exercise increases pain by 3 points on a 10-point scale in those with fibromyalgia (FM) (Fig. 2A),²³ and isometric contractions in individuals with FM show no increase in pain thresholds that normally occur in healthy controls.^{41,52} Furthermore, people with chronic pain are generally less active than age-matched healthy controls (Figs. 2B and C).^{20,29,55,59}

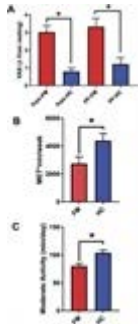


Figure 2. (A) Graphs showing the increase in pain and physical fatigue in people with fibromyalgia compared with healthy controls after a whole-body fatiguing exercise task. *P < 0.05. Data are mean ± SEM. Data are regraphed from Ref. 23. (B) Graph showing self-reported activity levels in METS*minute/week for those with fibromyalgia and healthy controls. *P < 0.05. Data are mean ± SEM. Data are graphic representations from tables in Ref. 59. (C) Graph showing moderate physical activity levels measured by accelerometry in fibromyalgia compared with healthy controls. *P < 0.05. Data are mean ± SEM. Data are graphic representations from tables in Ref. 59. FM, fibromyalgia; HC, healthy controls; METS, metabolic equivalents; PF, physical fatigue; VAS, visual analogue scale.

2. Effects of exercise on the central nervous system

We propose that regular physical activity changes the state of central pain inhibitory pathways and the immune system to result in a protective effect against a peripheral insult. This normal protective state that

occurs with regular physical activity is not found in physically inactive individuals and results in a greater risk of the development of chronic long-lasting pain.

[Figure 3](#) depicts 2 states of the nervous system for cells in the brainstem, which modulate pain. Brainstem sites, such as the rostral ventromedial medulla (RVM), both facilitate and inhibit nociceptive signals.[37,70](#) We suggest that in the sedentary condition, muscle insult results in increased phosphorylation of the NR1 subunit of the *N*-methyl-D-aspartate (NMDA) receptor, which would result in increased facilitation. There is substantial research suggesting that NMDA receptors in the RVM facilitate pain, and phosphorylation of the NMDA receptor enhances channel conductance and increases insertion of NMDA receptors into the synapse.[18,21,22,27,81,86,87](#) Simultaneously, we propose that there is an increased expression of the serotonin transporter (SERT), which would result in reduced inhibition. Classic studies show that injection of serotonin or a SERT inhibitor into the RVM is analgesic, blockade of serotonin receptors prevents analgesia by stimulation of the periaqueductal gray, and systemic morphine increases serotonin in the RVM.[47,48,56,57,78](#) Furthermore, in the sedentary condition, there is less opioid tone in the nervous system to prevent these excitatory effects. In the physically active state, we propose that activation of opioid receptors modulates neuron activity so that there is less phosphorylation of the NMDA receptor and less expression of the SERT. Basic research studies support this hypothesis. We show, in sedentary animals, that there is increased expression of the SERT and increased phosphorylation of the NR1 subunit of the NMDA receptor in the RVM in animals with nerve injury or chronic muscle pain.[2,8,54](#) These increases do not occur in physically active animals with nerve injury or chronic muscle pain.[2,8,54](#) Further blockade of opioid receptors systemically, in the periaqueductal gray or the RVM, prevents the protective effects of regular physical activity, and mu-opioid receptor knockouts do not develop analgesia to regular physical activity.[54](#) Furthermore, we show that naloxone-treated or mu-opioid receptor knockout physically active animals do not show the increases in SERT in the RVM, supporting an interaction between endogenous opioids and serotonin.[54](#) In human studies, greater exercise-induced analgesia was associated with a gene for stronger opioid signaling (OPRM1 G) in combination with weak 5-HT tone (5-HTT low/5-HT1a G), suggesting interactions between opioid and serotonergic mechanisms for exercise-induced analgesia.[82](#) Thus, regular physical activity prevents hyperalgesia through activation of opioids and serotonin to produce analgesia.

In humans, several studies have emerged suggesting that greater physical activity is associated with equal or reduced pain sensitivity across a wide range of assessments. Quantitative sensory testing is increasingly used as an indirect measure of centrally mediated pain processing. Healthy individuals routinely participating in vigorous activity demonstrate enhanced conditioned pain modulation, a measure of central pain inhibition, compared with less active individuals.[32,66](#) In people with osteoarthritis, a 12-week exercise program increased pain thresholds and decreased temporal summation.[38](#) However, in 1 study, temporal summation, a measure of central pain facilitation, to cold pain was unchanged,[32](#) whereas temporal summation to heat pain was reduced.[66](#) Similarly, a meta-analysis of athletes vs normally active adults indicates reduced pain sensitivity overall in athletes.[79](#) These studies suggest that engagement in regular physical activity is related to decreased pain sensitivity in healthy adults. However, few studies have examined associations between daily lifestyle physical activity and pain sensitivity in FM or other chronic pain populations.

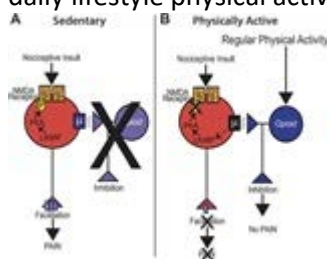


Figure 3. A schematic diagram representing the neurons in the brainstem, rostral ventromedial medulla, that facilitates and those that inhibits pain and how sedentary lifestyle (A) or physical activity (B) could modulate their activity. Based on data outlined in the text, we propose that in sedentary conditions, there is less opioid tone in the brainstem and overall less inhibition. This results in the neurons showing more facilitation after

nociceptive input with increases in phosphorylation of the NR1 subunit of the NMDA receptor and increased expression of the serotonin transporter. We further propose that regular physical activity increases release of endogenous opioids in the brainstem, which inhibit facilitatory neurons to reduce facilitation. This would be associated with less phosphorylation of the NR1 subunit of the NMDA receptor and reduced expression of serotonin transporter. Overall, in the physically active condition, there would be more inhibition from opioids and serotonin, and less excitation. NMDA, N-methyl-d-aspartate.

Epidemiological investigations also support the protective nature of physical activity on the development of chronic pain, which may be due to peripheral or central mechanisms. A population-based study from Norway showed that chronic musculoskeletal pain incidence was 10% to 38% less in individuals participating in moderate leisure-time activity 1 to 3 times per week compared to those with no leisure-time activity.^{50,51} However, in patient populations, the relationships between regular physical activity and central pain processing are less clear. Increasing physical activity and exercise reduces symptomology in a variety of patient population, and is a first-line treatment in a number of chronic pain populations, from FM to LBP.^{58,71} Furthermore, nonpharmacological therapies, in general, are considered first-line treatments, with exercise having strong support.^{58,71} However, quantitative sensory testing and physical activity levels have not been routinely investigated in patient populations. In a small study of 18 women with FM, fitness levels, as assessed by cycle ergometry or the 6-minute walk test, were not associated with pain thresholds or temporal summation assessments.²⁵ However, this area of study remains sparse and may be limited by the reduced range of lifestyle physical activity levels observed in many chronic pain populations.

3. Effects of exercise on the immune system

We also propose that regular physical activity modulates the immune system locally at the site of insult, systemically, and in the central nervous system. In the physically inactive condition, there are more inflammatory cytokines and less anti-inflammatory cytokines. After regular physical activity, this balance shifts to more anti-inflammatory cytokines and less inflammatory cytokines. Inflammatory cytokines activate receptors on nociceptors to produce pain, whereas anti-inflammatory cytokines reduce activity of nociceptors to prevent pain.^{26,33,46,90} Figure 4 shows our theory that physical activity levels modulate phenotype of macrophages in muscle. Macrophages are located in muscle and release inflammatory or anti-inflammatory cytokines depending on 2 relevant phenotypes: classically activated (M1) macrophages release inflammatory cytokines and regulatory (M2) macrophages release anti-inflammatory cytokines.⁶⁵ In support, we show that in uninjured animals, physically active animals show an increased proportion of M2 macrophages.⁵³ Similarly, in animals with nerve injury, sedentary animals show an increased proportion of M1 and less M2 macrophages at the site of injury, whereas physically active animals show increases in M2 and less M1 macrophages.³ The analgesia produced by regular physical activity and exercise is prevented by blockade of either IL-10 (muscle insult) or IL-4 (nerve injury).^{3,53} Thus, at the peripheral site of insult, there are alterations in macrophage phenotype that underlies the analgesia produced by regular exercise.

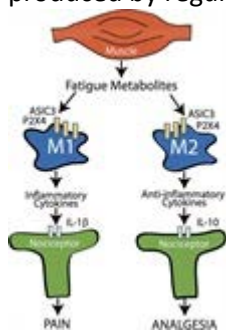


Figure 4. A schematic diagram representing the interaction between muscle, macrophages, and nociceptors in the peripheral nervous system. Macrophages, found in local tissue, can be polarized to an M1 phenotype that releases proinflammatory cytokines that activate nociceptors, or an M2 phenotype that releases anti-inflammatory cytokines that inhibit nociceptors. Our data support that there are greater M1

macrophages at the site of insult or injury in the sedentary state and that regular physical activity increases the proportion of M2 macrophages. Our data further support the notion that regular physical activity changes the state of the immune system so that there is a greater proportion of M2 macrophages and greater anti-inflammatory cytokine that mediates the analgesia of regular physical activity.

In chronic pain conditions, systemic inflammation is suggested as an underlying pathology.[60,75,76](#) Systemically, immune cells, ie, peripheral blood mononuclear cells are highly plastic, can alter levels of cytokines systemically or locally in tissue, and secrete inflammatory or anti-inflammatory cytokines based on their phenotype. In support, people with FM show enhanced circulating inflammatory cytokines and enhanced evoked release of inflammatory cytokines from circulating monocytes.[5,6,30,67,68](#) By contrast, a 4- or 8-month aquatic exercise program for individuals with FM decreases circulating and stimulated release from monocytes of inflammatory cytokines of IL-8, IL-1[beta], and tumor necrosis factor.[5,67,68](#) In healthy controls, exercise training also reduces the percentage of inflammatory monocytes in healthy men and women.[80](#) However, it should be noted that the number of subjects in most of these studies was low, and there are mixed results in the literature, likely a result of low sample size, use of mixed populations of immune cells, use of different stimuli to evoke cytokine release from immune cells.[61,76,83](#) Thus, preliminary studies show that exercise can alter systemic cytokines, and reduce systemic inflammation, a proposed mechanism of chronic pain.

In the central nervous system, glia cells modulate inflammatory and anti-inflammatory cytokines, and play a significant role in a variety of pain conditions.[62](#) In animals with nerve injury, there is activation of glial cells, increases in inflammatory cytokines, and decreases in anti-inflammatory cytokines.[3,34,62,85](#) Regular physical activity and exercise reduce glial cell activation, reduce inflammatory cytokines, and increase anti-inflammatory cytokines in the spinal cord dorsal horn.[3,34](#) Specifically, the enhanced astrocyte (glial fibrillary acidic protein) and microglial (Iba-1) immunoreactivity produced by nerve injury was significantly reduced by treadmill running.[3](#) In parallel, decreases in the anti-inflammatory cytokines-IL-4, IL-1ra, and IL-5-induced by nerve injury are reversed by treadmill running.[3](#) On the other hand, the increase in inflammatory cytokine IL-1beta is reduced by regular physical activity.[34](#) Furthermore, there are increases in transcription factors that regulate IL-1[beta], NF[kappa]B, and NLRP3 inflammasome, which are also reduced by regular physical activity.[34](#) Thus, regular exercise normalizes neuroimmune signaling in the central nervous system to prevent and reverse the development of hyperalgesia.

4. Effects of exercise on psychological comorbidities

In addition to the beneficial effects of exercise on immune health, people who participate in regular physical activity typically have enhanced mental health and psychological well-being, whereas individuals who are physically inactive are more likely to experience depression and anxiety. Specific to chronic pain, individuals who report low levels of physical activity are more likely to report higher kinesiophobia, fear avoidance beliefs, and pain catastrophizing compared with those who report higher physical activity levels.[28,49](#) However, in a cohort of patients with nonspecific LBP, fear of movement was not associated with subjective and objective (ie, questionnaire and accelerometry, respectively) measures of physical activity.[17](#) Therefore, the relation between physical activity and psychological health is less clear for individuals with chronic pain.

Despite the frequent recommendation of exercise in the treatment of depression and anxiety,[16,19](#) the prescription of exercise on improving psychological functioning for individuals with chronic pain is equivocal. In an overview of Cochrane Reviews to determine the effectiveness of physical activity and exercise interventions for adults with chronic pain,[31](#) only 5 of the 21 reviews included psychological well-being (ie, mental health, anxiety, and depression). Variable effects were reported, which included positive and no effects of exercise on psychological health.

The variability in the response may be related to how exercise is incorporated with other interventions in promoting psychological well-being. For example, in a systematic review and meta-analysis, the strongest

effects for reducing pain catastrophizing in adults with chronic noncancer pain were with multimodal treatment that included cognitive behavioral therapy and exercise.⁷⁴ The authors propose several explanations such that participating in exercise produces positive benefits that subsequently promote cognitive restructuring, increases self-efficacy by encouraging self-management, attenuates rumination through increased attentional demands of exercise, and decreases pain through activation of descending inhibitory systems. Similarly, in patients with chronic LBP, a multimodal program that included cognitive behavioral training and exercise produced better effects than exercise alone in improving quality of life and reducing disability and fear avoidance beliefs.⁶⁴ It is important to note that improvements occur with exercise alone; participating in regular physical activity that included both aerobic and strength training reduced pain catastrophizing in patients with chronic LBP, which mediated the improvements in disability and depression.⁷⁷ Thus, exercise prescription that incorporates a biopsychosocial approach that addresses the multitude of factors that occur with prolonged pain is important to maximize the overall positive effects.^{4,40}

5. Clinical implications

Pain with activity is a significant barrier to activity participation.¹¹⁻¹³ We routinely show that in sedentary animals, there is an increase in hyperalgesia with a single bout of fatiguing exercise.^{11,35,36,88} We further show that in human subjects, there is a significant increase in pain with fatiguing exercise in people with FM.²³ Treatments designed to reduce pain with activity have the potential to improve participation in regular activity. We recently show that application of transcutaneous electrical nerve stimulation (TENS) to the spine in people with FM reduces movement-evoked pain but has no effect on resting pain.²⁴ Similarly, in people with postoperative pain, Rakel and Frantz ⁷² applied TENS and showed a reduction in movement-evoked pain but not in resting pain. Thus, TENS may be an effective treatment to reduce movement-evoked pain to encourage activity participation in individuals with chronic pain.

The type of exercise may be less important than the act of doing exercise. Several studies have compared different types of exercise for different types of pain and show no difference between active exercise interventions.^{15,39,45,73} For example, in individuals with LBP, comparison of spinal stabilization exercises to conventional physical therapy that included general exercise showed no differences between groups.¹⁴ For those with neck pain, comparison of proprioceptive training to craniocervical flexion showed no differences in outcomes between groups.⁴⁵ Similarly, comparison of graded exercise and graded exposure for those with chronic LBP showed similar effects.¹⁵ Furthermore, significant effects of strengthening and aerobic exercise are shown in LBP, osteoarthritis, and FM, and are both part of recommended guidelines for these conditions.^{1,9,10,12,58,71} In fact, a recent Cochrane review comparing motor control exercise with other forms of exercise for those with chronic LBP concluded "Given the evidence that motor control exercise is not superior to other forms of exercise, the choice of exercise for LBP should probably depend on patient and therapist preferences, therapist training, costs, and safety."⁷³ We suggest that this lack of specificity of exercise may be related to the multiple and widespread mechanisms by which exercise works to reduce pain.

6. Future research directions

Basic science studies have only just begun to examine the underlying mechanisms of exercise. A better understanding of the molecular and cellular mechanisms of how exercise can lead increase pain or decrease pain will help to develop novel strategies to address chronic pain and improve implementation and adherence for this important intervention for chronic pain. It is abundantly clear that regular exercise and physical activity are effective for reduction in pain. It has also become increasingly clear that the type of exercise for reduction in pain is less important than doing the exercise. Although the CDC recommends 150 minutes of moderate physical activity per week and 2 days of strengthening per week for health benefits,¹³ it is unclear whether this dose is needed for pain relief.⁴ Indeed, multiple clinical trials use less time and lower intensities and still produce clinical effects in those with chronic pain.⁴⁰ However, we do not know the most effective dose, or the minimal effective dose. Furthermore, like all interventions, adherence and compliance with the program is extremely important to producing an effect. Barriers to exercise adherence include pain with

exercise, low levels of physical activity, low self-efficacy, psychological dysfunction, and poor social support.⁴³ Supervised exercise, individualized therapy, and self-management techniques may improve adherence; however, the quality of trials assessing these interventions is low.⁴⁴ Thus, future clinical studies will need to determine the most effective and minimally effective doses of exercise, if physical activity is equally beneficial to regular prescribed exercise, and develop methods and programs to improve adherence. Finally, although accepted that exercise is an important intervention for chronic pain, it is often not used as a first-line treatment, relying rather on medication prescriptions. The CDC opioid prescribing guidelines recommend the use of nonpharmacological approaches as the preferred approach to chronic pain (CDC guidelines). As much as 50% of all visits to primary care practitioners are for chronic pain,⁷ yet nonpharmacological treatments are underutilized. Therefore, future studies should develop innovative methods to improve utilization of nonpharmacological treatments by health care practitioners for both acute and chronic pain.

Conflict of interest statement

The authors have no conflict of interest to declare.

References

- [1]. Bidonde J, Busch AJ, Schachter CL, Overend TJ, Kim SY, Goes SM, Boden C, Foulds HJ. Aerobic exercise training for adults with fibromyalgia. *Cochrane Database Syst Rev* 2017;6:CD012700.
- [2]. Bobinski F, Ferreira TA, Cordova MM, Dombrowski PA, da CC, Santo CC, Poli A, Pires RG, Martins-Silva C, Sluka KA, Santos AR. Role of brainstem serotonin in analgesia produced by low-intensity exercise on neuropathic pain after sciatic nerve injury in mice. *PAIN* 2015;156:2595–606.
- [3]. Bobinski F, Teixeira JM, Sluka KA, Santos ARS. Interleukin-4 mediates the analgesia produced by low-intensity exercise in mice with neuropathic pain. *PAIN* 2018;159:437–50.
- [4]. Booth J, Moseley GL, Schiltenswolf M, Cashin A, Davies M, Hubscher M. Exercise for chronic musculoskeletal pain: a biopsychosocial approach. *Musculoskeletal Care* 2017;15:413–21.
- [5]. Bote ME, Garcia JJ, Hinchado MD, Ortega E. An exploratory study of the effect of regular aquatic exercise on the function of neutrophils from women with fibromyalgia: role of IL-8 and noradrenaline. *Brain Behav Immun* 2013;39:107–12.
- [6]. Bote ME, Garcia JJ, Hinchado MD, Ortega E. Fibromyalgia: anti-inflammatory and stress responses after acute moderate exercise. *PLoS One* 2013;8:e74524.
- [7]. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006;10:287–333.
- [8]. Brito RRL, Sluka KA. Regular physical activity prevents development of chronic muscle pain through modulation of supraspinal opioid and serotonergic mechanisms. *Pain Rep* 2017;2:e618.
- [9]. Brosseau L, Taki J, Desjardins B, Thevenot O, Fransen M, Wells GA, Mizusaki Imoto A, Toupin-April K, Westby M, Alvarez Gallardo IC, Gifford W, Laferrriere L, Rahman P, Loew L, De Angelis G, Cavallo S, Shallwani SM, Aburub A, Bennell KL, Van der Esch M, Simic M, McConnell S, Harmer A, Kenny GP, Paterson G, Regnaud JP, Lefevre-Colau MM, McLean L. The Ottawa panel clinical practice guidelines for the management of knee osteoarthritis. Part three: aerobic exercise programs. *Clin Rehabil* 2017;31:612–24.
- [10]. Brosseau L, Taki J, Desjardins B, Thevenot O, Fransen M, Wells GA, Mizusaki Imoto A, Toupin-April K, Westby M, Alvarez Gallardo IC, Gifford W, Laferrriere L, Rahman P, Loew L, De Angelis G, Cavallo S, Shallwani SM, Aburub A, Bennell KL, Van der Esch M, Simic M, McConnell S, Harmer A, Kenny GP, Paterson G, Regnaud JP, Lefevre-Colau MM, McLean L. The Ottawa panel clinical practice guidelines for the management of knee osteoarthritis. Part two: strengthening exercise programs. *Clin Rehabil* 2017;31:596–611.
- [11]. Burnes LA, Kolker SJ, Danielson JF, Walder RY, Sluka KA. Enhanced muscle fatigue occurs in male but not female ASIC3^{-/-} mice. *Am J Physiol Regul Integr Comp Physiol* 2008;294:R1347–55.

- [12]. Busch AJ, Webber SC, Richards RS, Bidonde J, Schachter CL, Schafer LA, Danyliw A, Sawant A, Dal Bello-Haas V, Rader T, Overend TJ. Resistance exercise training for fibromyalgia. *Cochrane Database Syst Rev* 2013;12:CD010884.
- [13]. Centers for Disease Control and Prevention. How much physical activity do adults need? 2016. Available at: https://www.cdc.gov/cancer/dccp/prevention/policies_practices/physical_activity/guidelines.htm. Accessed February 2018.
- [14]. Cairns BE, Svensson P, Wang K, Castrillon E, Hupfeld S, Sessle BJ, rendt-Nielsen L. Ketamine attenuates glutamate-induced mechanical sensitization of the masseter muscle in human males. *Exp Brain Res* 2006;169:467–72.
- [15]. Calley DQ, Jackson S, Collins H, George SZ. Identifying patient fear-avoidance beliefs by physical therapists managing patients with low back pain. *J Orthop Sports Phys Ther* 2010;40:774–83.
- [16]. Carek PJ, Laibstain SE, Carek SM. Exercise for the treatment of depression and anxiety. *Int J Psychiatry Med* 2011;41:15–28.
- [17]. Carvalho FA, Maher CG, Franco MR, Morelhao PK, Oliveira CB, Silva FG, Pinto RZ. Fear of movement is not associated with objective and subjective physical activity levels in chronic nonspecific low back pain. *Arch Phys Med Rehabil* 2017;98:96–104.
- [18]. Chen BS, Braud S, Badger JD, Isaac JT, Roche KW. Regulation of NR1/NR2C N-methyl-D-aspartate (NMDA) receptors by phosphorylation. *J Biol Chem* 2006;281:16583–90.
- [19]. Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, McMurdo M, Mead GE. Exercise for depression. *Cochrane Database Syst Rev* 2013:CD004366.
- [20]. Cooper NA, Rakel BA, Zimmerman B, Tonelli SM, Herr KA, Clark CR, Noiseux NO, Callaghan JJ, Sluka KA. Predictors of multidimensional functional outcomes after total knee arthroplasty. *J Orthop Res* 2017;35:2790–8.
- [21]. Coutinho SV, Urban MO, Gebhart GF. Role of glutamate receptors and nitric oxide in the rostral ventromedial medulla in visceral hyperalgesia. *PAIN* 1998;78:59–69.
- [22]. da Silva LFS, DeSantana JM, Sluka KA. Activation of NMDA receptors in the brainstem, rostral ventromedial medulla, and nucleus reticularis gigantocellularis mediates mechanical hyperalgesia produced by repeated intramuscular injections of acidic saline in rats. *PAIN* 2010;11:378–87.
- [23]. Dailey DL, Keffala VJ, Sluka KA. Cognitive and physical fatigue tasks enhance pain, cognitive fatigue and physical fatigue in people with fibromyalgia. *Arthritis Care Res (Hoboken)* 2015;67:288–96.
- [24]. Dailey DL, Rakel BA, Vance CG, Liebano RE, Amrit AS, Bush HM, Lee KS, Lee JE, Sluka KA. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. *PAIN* 2013;154:2554–62.
- [25]. de Bruijn ST, van Wijck AJ, Geenen R, Snijders TJ, van der Meulen WJ, Jacobs JW, Veldhuijzen DS. Relevance of physical fitness levels and exercise-related beliefs for self-reported and experimental pain in fibromyalgia: an explorative study. *J Clin Rheumatol* 2011;17:295–301.
- [26]. Dina OA, Levine JD, Green PG. Enhanced cytokine-induced mechanical hyperalgesia in skeletal muscle produced by a novel mechanism in rats exposed to unpredictable sound stress. *Eur J Pain* 2011;15:796–800.
- [27]. Ehlers MD, Tingley WG, Haganir RL. Regulated subcellular distribution of the NR1 subunit of the NMDA receptor. *Science* 1995;269:1734–7.
- [28]. Elfving B, Andersson T, Grooten WJ. Low levels of physical activity in back pain patients are associated with high levels of fear-avoidance beliefs and pain catastrophizing. *Physiother Res Int* 2007;12:14–24.
- [29]. Ellingson LD, Shields MR, Stegner AJ, Cook DB. Physical activity, sustained sedentary behavior, and pain modulation in women with fibromyalgia. *J Pain* 2012;13:195–206.
- [30]. Garcia JJ, Cidoncha A, Bote ME, Hinchado MD, Ortega E. Altered profile of chemokines in fibromyalgia patients. *Ann Clin Biochem* 2013;51:576–81.
- [31]. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2017;4:CD011279.

- [32]. Geva N, Defrin R. Enhanced pain modulation among triathletes: a possible explanation for their exceptional capabilities. *PAIN* 2013;154:2317–23.
- [33]. Gong WY, Abdelhamid RE, Carvalho CS, Sluka KA. Resident macrophages in muscle contribute to development of hyperalgesia in a mouse model of non-inflammatory muscle pain. *J Pain* 2016;17:1081–94.
- [34]. Grace PM, Fabisiak TJ, Green-Fulham SM, Anderson ND, Strand KA, Kwilasz AJ, Galer EL, Walker FR, Greenwood BN, Maier SF. Prior voluntary wheel running attenuates neuropathic pain. *PAIN* 2016;157:2012–23.
- [35]. Gregory NS, Brito R, Fusaro MC, Sluka KA. ASIC3 is required for development of fatigue-induced hyperalgesia. *Mol Neurobiol* 2016;53:1020–30.
- [36]. Gregory NS, Gibson-Corley K, Frey-Law L, Sluka KA. Fatigue-enhanced hyperalgesia in response to muscle insult: induction and development occur in a sex-dependent manner. *PAIN* 2013;154:2668–76.
- [37]. Heinricher MM, Fields HL. Central nervous system mechanisms of pain modulation. In: McMahon SB, Koltzenburg M, Tracey I, Turk DC, editors. *Melzack and Wall's textbook of pain*. Philadelphia: Elsevier, 2013. pp. 129–42.
- [38]. Henriksen M, Klokke L, Graven-Nielsen T, Bartholdy C, Schjodt JT, Bandak E, Danneskiold-Samsøe B, Christensen R, Bliddal H. Association of exercise therapy and reduction of pain sensitivity in patients with knee osteoarthritis: a randomized controlled trial. *Arthritis Care Res (Hoboken)* 2014;66:1836–43.
- [39]. Henry SM, Van Dillen LR, Ouellette-Morton RH, Hitt JR, Lomond KV, DeSarno MJ, Bunn JY. Outcomes are not different for patient-matched versus nonmatched treatment in subjects with chronic recurrent low back pain: a randomized clinical trial. *Spine J* 2014;14:2799–810.
- [40]. Hoeger Bement MK, Sluka KA. Exercise-induced hypoalgesia: an evidence-based review. In: Sluka KA, editor. *Pain mechanisms and management for the physical therapist*. Philadelphia: Wolters Kluwer, 2016. pp. 177–202.
- [41]. Hoeger Bement MK, Weyer A, Hartley S, Drewek B, Harkins AL, Hunter SK. Pain perception after isometric exercise in women with fibromyalgia. *Arch Phys Med Rehabil* 2011;92:89–95.
- [42]. Hurley MV, Walsh NE, Mitchell H, Nicholas J, Patel A. Long-term outcomes and costs of an integrated rehabilitation program for chronic knee pain: a pragmatic, cluster randomized, controlled trial. *Arthritis Care Res (Hoboken)* 2012;64:238–47.
- [43]. Jack K, McLean SM, Moffett JK, Gardiner E. Barriers to treatment adherence in physiotherapy outpatient clinics: a systematic review. *Man Ther* 2010;15:220–8.
- [44]. Jordan JL, Holden MA, Mason EE, Foster NE. Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev* 2010:CD005956.
- [45]. Jull G, Falla D, Treleaven J, Hodges P, Vicenzino B. Retraining cervical joint position sense: the effect of two exercise regimes. *J Orthop Res* 2007;25:404–12.
- [46]. Kanaan SA, Poole S, Saade NE, Jabbur S, Safieh-Garabedian B. Interleukin-10 reduces the endotoxin-induced hyperalgesia in mice. *J Neuroimmunol* 1998;86:142–50.
- [47]. Kiefel JM, Cooper ML, Bodnar RJ. Inhibition of mesencephalic morphine analgesia by methysergide in the medial ventral medulla of rats. *Physiol Behav* 1992;51:201–5.
- [48]. Kiefel JM, Cooper ML, Bodnar RJ. Serotonin receptor subtype antagonists in the medial ventral medulla inhibit mesencephalic opiate analgesia. *Brain Res* 1992;597:331–8.
- [49]. Koho P, Orenius T, Kautiainen H, Haanpää M, Pohjolainen T, Hurri H. Association of fear of movement and leisure-time physical activity among patients with chronic pain. *J Rehabil Med* 2011;43:794–9.
- [50]. Landmark T, Romundstad P, Borchgrevink PC, Kaasa S, Dale O. Associations between recreational exercise and chronic pain in the general population: evidence from the HUNT 3 study. *PAIN* 2011;152:2241–7.
- [51]. Landmark T, Romundstad PR, Borchgrevink PC, Kaasa S, Dale O. Longitudinal associations between exercise and pain in the general population—the HUNT pain study. *PLoS One* 2013;8:e65279.
- [52]. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. *PAIN* 2010;151:77–86.

- [53]. Leung A, Gregory NS, Allen LA, Sluka KA. Regular physical activity prevents chronic pain by altering resident muscle macrophage phenotype and increasing IL-10 in mice. *PAIN* 2016;157:79.
- [54]. Lima LV, DeSantana JM, Rasmussen LA, Sluka KA. Short-duration physical activity prevents the development of activity-induced hyperalgesia through opioid and serotonergic mechanisms. *PAIN* 2017;158:1697–710.
- [55]. Lin CW, McAuley JH, Macedo L, Barnett DC, Smeets RJ, Verbunt JA. Relationship between physical activity and disability in low back pain: a systematic review and meta-analysis. *PAIN* 2011;152:607–13.
- [56]. Llewelyn M, Azami J, Roberts M. The effect of modification of 5-hydroxytryptamine function in nucleus raphe magnus on nociceptive threshold. *Brain Res* 1984;306:165–70.
- [57]. Llewelyn MB, Azami J, Roberts MHT. Effects of 5-hydroxytryptamine applied into the nucleus raphe magnus on nociceptive thresholds and neuronal firing rate. *Brain Res* 1983;258:59–68.
- [58]. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Hauser W, Fluss E, Choy E, Kosek E, Amris K, Branco J, Dincer F, Leino-Arjas P, Longley K, McCarthy GM, Makri S, Perrot S, Sarzi-Puttini P, Taylor A, Jones GT. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis* 2017;76:318–28.
- [59]. McLoughlin MJ, Colbert LH, Stegner AJ, Cook DB. Are women with fibromyalgia less physically active than healthy women? *Med Sci Sports Exerc* 2011;43:905–12.
- [60]. Mendieta D, la Cruz-Aguilera DL, Barrera-Villalpando MI, Becerril-Villanueva E, Arreola R, Hernandez-Ferreira E, Perez-Tapia SM, Perez-Sanchez G, Garcés-Alvarez ME, Aguirre-Cruz L, Velasco-Velazquez MA, Pavon L. IL-8 and IL-6 primarily mediate the inflammatory response in fibromyalgia patients. *J Neuroimmunol* 2016;290:22–5.
- [61]. Menzies V, Lyon DE. Integrated review of the association of cytokines with fibromyalgia and fibromyalgia core symptoms. *Biol Res Nurs* 2010;11:387–94.
- [62]. Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. *Nat Rev Neurosci* 2009;10:23–36.
- [63]. Mogren IM. Previous physical activity decreases the risk of low back pain and pelvic pain during pregnancy. *Scand J Public Health* 2005;33:300–6.
- [64]. Monticone M, Ferrante S, Rocca B, Baiardi P, Farra FD, Foti C. Effect of a long-lasting multidisciplinary program on disability and fear-avoidance behaviors in patients with chronic low back pain: results of a randomized controlled trial. *Clin J Pain* 2013;29:929–38.
- [65]. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. *Nat Rev Immunol* 2008;8:958–69.
- [66]. Naugle KM, Riley JL III. Self-reported physical activity predicts pain inhibitory and facilitatory function. *Med Sci Sports Exerc* 2014;46:622–9.
- [67]. Ortega E, Bote ME, Giraldo E, Garcia JJ. Aquatic exercise improves the monocyte pro- and anti-inflammatory cytokine production balance in fibromyalgia patients. *Scand J Med Sci Sports* 2012;22:104–12.
- [68]. Ortega E, Garcia JJ, Bote ME, Martin-Cordero L, Escalante Y, Saavedra JM, Northoff H, Giraldo E. Exercise in fibromyalgia and related inflammatory disorders: known effects and unknown chances. *Exerc Immunol Rev* 2009;15:42–65.
- [69]. Pedersen BK. The disease of physical inactivity—and the role of myokines in muscle–fat cross talk. *J Physiol* 2009;587:5559–68.
- [70]. Porreca F, Ossipov MH, Gebhart G. Chronic pain and medullary descending facilitation. *Trends Neurosciences* 2002;25:319–25.
- [71]. Qaseem A, Wilt TJ, McLean RM, Forcica MA. Clinical guidelines committee of the American college of P. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American college of physicians. *Ann Intern Med* 2017;166:514–30.
- [72]. Rakel B, Frantz R. Effectiveness of transcutaneous electrical nerve stimulation on postoperative pain with movement. *J Pain* 2003;4:455–64.
- [73]. Saragiotto BT, Maher CG, Yamato TP, Costa LO, Menezes Costa LC, Ostelo RW, Macedo LG. Motor control exercise for chronic non-specific low-back pain. *Cochrane Database Syst Rev* 2016:CD012004.

- [74]. Schutze R, Rees C, Smith A, Slater H, Campbell JM, O'Sullivan P. How can we best reduce pain catastrophizing in adults with chronic noncancer pain? A systematic review and meta-analysis. *J Pain* 2018;19:233–56.
- [75]. Slade GD, Conrad MS, Diatchenko L, Rashid NU, Zhong S, Smith S, Rhodes J, Medvedev A, Makarov S, Maixner W, Nackley AG. Cytokine biomarkers and chronic pain: association of genes, transcription, and circulating proteins with temporomandibular disorders and widespread palpation tenderness. *PAIN* 2011;152:2802–12.
- [76]. Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. *Neuroscience* 2016;338:114–29.
- [77]. Smeets RJ, Vlaeyen JW, Kester AD, Knottnerus JA. Reduction of pain catastrophizing mediates the outcome of both physical and cognitive-behavioral treatment in chronic low back pain. *J Pain* 2006;7:261–71.
- [78]. Taylor BK, Basbaum AI. Systemic morphine-induced release of serotonin in the rostroventral medulla is not mimicked by morphine microinjection into the periaqueductal gray. *J Neurochem* 2003;86:1129–41.
- [79]. Tesarz J, Schuster AK, Hartmann M, Gerhardt A, Eich W. Pain perception in athletes compared to normally active controls: a systematic review with meta-analysis. *PAIN* 2012;153:1253–62.
- [80]. Timmerman KL, Flynn MG, Coen PM, Markofski MM, Pence BD. Exercise training-induced lowering of inflammatory (CD14+CD16+) monocytes: a role in the anti-inflammatory influence of exercise? *J Leukoc Biol* 2008;84:1271–8.
- [81]. Tingley WG, Roche KW, Thompson AK, Hagan RL. Regulation of NMDA receptor phosphorylation by alternative splicing of the C-terminal domain. *Nature* 1993;364:70–3.
- [82]. Tour J, Lofgren M, Mannerkorpi K, Gerdle B, Larsson A, Palstam A, Bileviciute-Ljungar I, Bjersing J, Martin I, Ernberg M, Schalling M, Kosek E. Gene-to-gene interactions regulate endogenous pain modulation in fibromyalgia patients and healthy controls-antagonistic effects between opioid and serotonin-related genes. *PAIN* 2017;158:1194–203.
- [83]. Uceyler N, Hauser W, Sommer C. Systematic review with meta-analysis: cytokines in fibromyalgia syndrome. *BMC Musculoskelet Disord* 2011;12:245.
- [84]. Wainwright JM. The influence of physical therapy in reducing disability time in fractures of the long bones. *Ann Surg* 1921;74:304–5.
- [85]. Watkins LR, Milligan ED, Maier SF. Spinal cord glia: new players in pain. *PAIN* 2001;93:201–5.
- [86]. Wei H, Pertovaara A. MK-801, an NMDA receptor antagonist, in the rostroventromedial medulla attenuates development of neuropathic symptoms in the rat. *Neuroreport* 1999;10:2933–7.
- [87]. Xu M, Kim CJ, Neubert MJ, Heinricher MM. NMDA receptor-mediated activation of medullary pronociceptive neurons is required for secondary thermal hyperalgesia. *PAIN* 2007;127:253–62.
- [88]. Yokoyama T, Audette KM, Sluka KA. Pregabalin reduces muscle and cutaneous hyperalgesia in two models of chronic muscle pain in rats. *J Pain* 2007;8:422–9.
- [89]. Zhang R, Chomistek AK, Dimitrakoff JD, Giovannucci EL, Willett WC, Rosner BA, Wu K. Physical activity and chronic prostatitis/chronic pelvic pain syndrome. *Med Sci Sports Exerc* 2015;47:757–64.
- [90]. Zheng W, Huang W, Liu S, Levitt RC, Candiotti KA, Lubarsky DA, Hao S. IL-10 mediated by herpes simplex virus vector reduces neuropathic pain induced by HIV gp120 combined with ddC in rats. *Mol Pain* 2014;10:49.