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MASTERCLASS

Modern pain neuroscience in clinical practice: applied to post-cancer, paediatric and sports-related pain



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Abstract

Background: In the last decade, evidence regarding chronic pain has developed exponentially. Numerous studies show that many chronic pain populations show specific neuroplastic changes in the peripheral and central nervous system. These changes are reflected in clinical manifestations, like a generalized hypersensitivity of the somatosensory system. Besides a hypersensitivity of bottom-up nociceptive transmission, there is also evidence for top-down facilitation of pain due to malfunctioning of the endogenous descending nociceptive modulatory systems. These and other aspects of modern pain neuroscience are starting to be applied within daily clinical practice. However, currently the application of this knowledge is mostly limited to the general adult population with musculoskeletal problems, while evidence is getting stronger that also in other chronic pain populations these neuroplastic processes may contribute to the occurrence and persistence of the pain problem. Therefore, this masterclass article aims at giving an overview of the current modern pain neuroscience knowledge and its potential application in post-cancer, paediatric and sports-related pain problems.

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Introduction

Modern pain neuroscience has raised the awareness that pain and tissue damage are not synonymous terms. Pain is often disproportionate to tissue damage and can even be reported without it. On the other hand, obvious tissue damage (and thus nociception) does not guarantee the actual feeling of pain either. Many chronic pain patients present a generalized hypersensitivity of the somatosensory system, often referred to as central sensitization.^{1–4} Central sensitization is not only present in typical chronic widespread pain conditions such as chronic fatigue syndrome⁵ and fibromyalgia,^{1,6} but is also known to be the underlying mechanism in at least a subgroup of patients with persistent low back pain,^{7,8} migraine,⁹ pelvic pain,^{10,11} tennis elbow,¹² subacromial impingement syndrome,¹³ post-cancer pain¹⁴ and rheumatoid arthritis.¹⁵

Central sensitization can include neuroplastic changes in both the peripheral and central nervous system. Besides increased neuronal responsiveness in the periphery and spinal cord (e.g., enhanced bottom-up signalling),^{16,17} an important role within the pathophysiology of central sensitization is reserved for malfunctioning of the endogenous descending nociceptive modulatory systems.^{18,19} The basis of this nociceptive modulatory system is situated in the brain, where it seems to present itself in a 'neurologic pain signature'. While several pain areas are involved in pain processing and modulation, certain cognitive styles and personality traits influence this system through complex collaboration between the prefrontal cortex, limbic system and periaqueductal grey among other brain areas.²⁰ In these and other nociceptive-processing brain areas, abnormalities in structure and function are described within several chronic pain populations.^{21–24} Nevertheless, evidence in several chronic pain populations indicates that these observed abnormalities are a reversible consequence of chronic pain rather than actual damage. In fact, recent studies investigating the effect of surgical interventions in chronic pain patients demonstrate for example that grey matter abnormalities subside with the cessation of pain.^{25,26} Moreover, conservative treatments such as physical therapy interventions are able to alter abnormalities of the central nervous system.^{27–30}

The current progress in pain neuroscience knowledge increases the need for its implementation in daily clinical practice. Not only is it relevant to understand the influencing mechanisms in chronic pain, the presence of central sensitization has also been identified as a predictor for poor therapy outcome.^{31–33} Therefore, targeting the processes underlying central sensitization becomes an important consideration in clinical practice. Several therapy modalities are suggested for chronic pain management, but the absolute first step should always comprise pain neuroscience education.^{34,35}

Pain neuroscience education includes explaining to patients that pain is an output product of the brain resulting from input from multiple central and peripheral nervous system processes and leading to the perception of threat rather than pain being a reflection of current tissue damage.³⁶ Pain neuroscience education intends to transfer that knowledge to patients, allowing them to understand their pain and hence to effectively cope with their pain.³⁶ Educating

the chronic pain patient on the neuroscience behind their symptoms has been shown to be both comprehensible and effective.^{37,38} Although pain neuroscience education is necessary to overcome initial treatment barriers (perceptual context of a patient related to the identity, cause and consequences of the illness) and to increase therapy compliance, effect sizes remain rather small.^{38–42} Therefore it should not be used as sole treatment, but rather as a component in an active therapy programme with special emphasis to maladaptive pain perceptions and cognitions.^{34,43}

In a manual (or musculoskeletal) therapy setting, this active component can easily be implemented by providing the usual exercise and treatment modalities adjusted with modern pain neuroscience. This includes a time-contingent approach where cognitions and perceptions related to the specific exercise are constantly assessed and addressed when necessary. Because of the rather accessible implementation in manual (or musculoskeletal) therapy, the application of modern pain neuroscience is to date mostly concentrated in this area of physical therapy. However, central sensitization is not limited to merely musculoskeletal pain in a general adult population, but has also been described in post-cancer,¹⁴ pediatric^{44–52} and sports-related pain problems.⁵³ Therefore, this masterclass article aims to provide a critical overview on the application of modern pain neuroscience in post-cancer, paediatric and sports-related pain.

Modern pain neuroscience applied to post-cancer pain

In addition to fatigue, pain is the most persistent symptom in cancer survivors.⁵⁴ Classification of cancer pain used to be a controversial issue.⁵⁵ In recent years, a paradigm shift towards a mechanisms-based approach has taken place in the field of cancer pain,⁵⁶ analogue to evolutions in other chronic pain conditions.^{57,58} For effective pain management, correct identification of the dominant type of pain may be beneficial. Patient-centred physical therapy for cancer pain, founded on a mechanisms-based classification of pain, has previously been shown to yield positive findings in a prospective case series.⁵⁹ Such mechanism-based pain classification includes the differentiation between nociceptive, neuropathic and central sensitization pain.^{56,60} Recently, a clinical method for classifying any pain as either predominant central sensitization pain, neuropathic or nociceptive pain² was adopted to the cancer survivor population,⁶¹ allowing clinicians to differentiate between these three pain types. Since neuropathic and mixed cancer pain (i.e., a mixture of nociceptive, neuropathic and/or central sensitization pain) are considered to be more difficult to treat than pure nociceptive pain,^{62,63} this is important for clinical practice. Furthermore, the classification of the correct pain mechanism is relevant regarding the choice of the cancer pain treatment.⁶³

In addition to the classification of the predominant pain mechanism, modern pain neuroscience provides ample options for innovation within the field of physical therapy for people with pain following cancer treatment, including innovative educational, stress management and exercise interventions.

Although most of the educational interventions for cancer patients are effective in relieving pain, they are primarily focused on biomedical pain management instructions (e.g., use of analgesics).⁶⁴ When providing education to patients following cancer treatment, implementation of contemporary pain neuroscience into the educational programme may result in a superior outcome. In a non-cancer population with pain, pain neuroscience education is not only welcomed very positively by patients,^{38,65} but also effective in changing pain beliefs and improving health status and pain coping strategies.^{38,41,42,65,66} However, studies examining the effectiveness of pain neuroscience education in patients following cancer treatment are needed, before its implementation into routine clinical practice can be advocated.

Second, the stress response system is capable of influencing nociceptive processing through various pathways.^{67–73} Stress can relieve pain, but this is not always the case in chronic pain patients (following cancer treatment). People who survived cancer typically sustained a long period of severe emotional (e.g., receiving the diagnosis of cancer, fear of dying) and physical (e.g., surgery, chemotherapy, radiotherapy) stress. Hence, it comes as no surprise that some people following cancer treatment present with exhausted stress response systems, including blunted cortisol responses to psychological stress,^{74,75} flatter diurnal cortisol rhythms⁷⁶ and lower heart rate variability.^{77,78} Given the lack of effective medical treatment to 'fix' the physiological stress response systems and the close link between stress and pain, it seems warranted to integrate stress management into the management of pain following cancer treatment. Stress management, varying from cognitive behavioural stress management to relaxation, cognitive restructuring and coping skills training, is an evidence-based intervention for patients following cancer treatment.^{79,80}

Finally, evidence shows that exercise therapy (comprising a combination of aerobic and strengthening exercise) is effective in decreasing aromatase inhibitors-induced arthralgia in breast cancer survivors.⁸¹ Looking at more generic analgesic effects of exercise therapy in people following cancer treatment, it was concluded that exercise might be effective in decreasing pain in this population.^{82,83} Emerging evidence suggests a role for central sensitization in explaining pain in a subgroup of patients following cancer treatment.^{14,78} The study of Cantarero et al. demonstrated that hydrotherapy resulted in a significant increase in pressure pain threshold levels of the affected and non-affected side in breast cancer survivors with hormone therapy-associated arthralgia.⁸⁴ This study yields preliminary evidence for the effectiveness of exercise therapy in the management of hypersensitivity of the nervous system in cancer survivors, but further studies using exercise therapy adopted to our current understanding of pain neuroscience, are needed.^{85,86}

Modern pain neuroscience applied to paediatric pain

Chronic pain (e.g., headache, abdominal pain, back pain and musculoskeletal pain) is one of the most distressing and debilitating problems in children and adolescents.^{87,88}

and many children suffer from multiple pain complaints at the same time.⁸⁷ These persistent pain problems mainly affect the children during activities of daily living,⁸⁹ leading to less participation in recreational activities, more school absence, academic impairments and difficulties in maintaining social contacts.^{87,90–93} Additionally, evidence shows that children with a history of childhood chronic pain or children who are repeatedly exposed to invasive medical procedures (e.g., lumbar punctures or bone marrow aspirations) may show a greater predisposition to chronic pain and are more likely to develop new and different types of pain into adulthood.^{93,94}

Treatment recommendations for children with chronic pain show many similarities to those available in adults. They are often treated with one or more of the following non-pharmacological treatment modalities: physical therapy, relaxation therapy, sleep and stress management.⁹⁵ Research from the psychological field favours the use of behavioural or cognitive behavioural therapy for many chronic pain conditions in children (chronic headache, recurrent abdominal pain, juvenile idiopathic arthritis and fibromyalgia).⁹⁶ Cognitive behavioural therapy focusses on the development of personal coping strategies, which help patients to solve current problems and change unhelpful patterns in cognitions (e.g., thoughts, beliefs, and attitudes), behaviours, and emotional regulation.⁹⁶ Modern pain neuroscience applied to the paediatric population goes beyond that by adding pain neuroscience education as a mandatory first step in the treatment programme, as it aims at reconceptualizing the underlying physiological problem of the child's pain so that an appropriate cognitive and behavioural response is more likely to follow. Without this tailored reconceptualization of the child's pain, cognitive and behavioural responses may be interpreted as counterintuitive to children and their parents.

Pain neuroscience education has been frequently studied in various adult chronic pain populations. However, to our knowledge, no study examined its effectiveness in the context of paediatric pain. Yet, based on the following reasons, the use of pain neuroscience education might be beneficial in this particular population. Firstly, emerging empirical inquiry suggests that central sensitization might be present in children with chronic pain.^{44–52} More specifically, manifestations of central sensitization, such as secondary hyperalgesia and altered cortical nociceptive processing were found in children with recurrent abdominal pain, juvenile idiopathic arthritis, juvenile fibromyalgia and migraine. Secondly, children and their parents might develop negative pain cognitions when they do not understand the origin of their (child's) pain complaints. Based on previous findings that a better understanding of the nature of the illness results in improved patient outcomes,⁹⁷ both child and parents should be involved in pain neuroscience education applied to children. Taking this into account, as well as the possible contribution of central sensitization in several chronic pain conditions in children, education should include explanation and reassurance about the cause of pain, a brief summary of relevant pain mechanisms and the integral role of psychosocial and physical factors in precipitating and maintaining pain. As such, pain neuroscience education, which contains this main content, might be recommended in children with chronic pain. Still, studies should

investigate the effectiveness of pain neuroscience education in this particular population, in order to support its implementation into routine clinical practice.

As mentioned before, treatment prescriptions for children with chronic pain often include physical therapy.⁹⁵ Research supports this recommendation, by showing significantly improved pain outcomes following early dedicated therapy in children with neuropathic pain,⁹⁸ musculoskeletal pain,⁹⁹ low back pain,¹⁰⁰ hypermobility with pain¹⁰¹ and arthritis.¹⁰² Because of its beneficial effects on pain, physical therapy and exercise programmes should be encouraged, especially since children with chronic pain tend to be less physically active than their peers.⁹¹ Consequently, this population might be at higher risk to become deconditioned.

At present, physical therapy goals for children with chronic pain are usually derived from a pure biomedical (e.g., aerobic and neuromuscular training) or psychosocial point of view (e.g., behavioural or cognitive behavioural therapy). Still, neither of these approaches enclose our current understanding of modern pain neuroscience. Further research should investigate the beneficial effects of therapeutic pain neuroscience education on preparing these children for physical therapy and a cognition-targeted, time-contingent approach to daily physical activity.

Modern pain neuroscience applied to sports-related pain

Sports or physical exercise improves health and wellbeing. However, most athletes will get injured at a certain point in time.^{103,104} The prevalence of injuries in sports is high and pain is the most common injury-related symptom. Consequences are disability and, for athletes most important, time loss from sports activities. Several classifications and models have been used to describe and define sports injuries and their aetiology.¹⁰⁵

Trauma or overuse are often the identified cause in athletic injury. Applying the proposed classification system in modern neuroscience (nociceptive pain, neuropathic pain and central sensitization pain), most of the traumatic injuries would be related to nociceptive input, while overuse or repetitive injuries could be related to central sensitization pain. To date, the aetiology of overuse or repetitive injuries has mostly been related to biomechanical factors such as technique, posture, training load and competition exposure.^{106–109} However, the exact pathogenesis underlying the development of pain in many overuse or repetitive injuries still remains unclear. Therefore, it could be useful to consider whether central sensitization could be an explanatory factor.

One of the first studies relating overuse injuries to central pain mechanisms found that in a group of different athletic overuse injuries 27% showed signs of central sensitization.¹¹⁰ Following this study more research was conducted, with special emphasis to the field of tendinopathy. Persistent tendinopathies can be classified as overuse injuries and are most often not related to clear tissue damage or nociceptive input.¹¹¹ In a recent meta-analysis signs of central sensitization were found in upper-limb tendinopathies⁵³ while evidence in lower-limb tendinopathies was more conflicting.^{112–114} Still, other

studies found reduced two-point discrimination in patients with Achilles tendinopathy,¹¹⁵ which is suggestive for reorganization of the somatosensory cortex. Overall, there is growing evidence that central sensitization is present in at least a subgroup of patients with sports-related problems and thus modern pain neuroscience might also be applicable in the field of sport related pain (especially regarding tendon injuries).

Another important focus within modern pain neurosciences is the association between pain and psychosocial aspects. Numerous studies support the importance of psychosocial variables in athletic injuries.¹¹⁶ A recent review on the association of tendinopathy and psychosocial factors concluded that clinicians should use validated tools to assess psychosocial variables in injured athletes to take them into account during rehabilitation.¹¹⁷ Athletes and coaches appear to accept this approach since they have a broad biopsychosocial perspective on the onset and maintenance of overuse injuries.¹¹⁸

The trend to consider psychosocial factors in sport sciences could also be valuable in optimizing strategies for successful return to play.^{119,120} A failed return to play could be seen in light of chronicity and recurrence. Recent literature provides evidence that psychosocial factors such as fear and catastrophizing have predictive value in therapy outcome.^{121–127} Fear of re-injury is not only a predictor, but also a contributor to predict return to sports.^{122,128} Additionally, pain catastrophizing contributes to the patients symptomatology, in which higher pain catastrophizing scores are associated with higher pain sensations.¹²⁵ Within the fear-avoidance model, both fear and catastrophizing can be precursors of avoidant behaviour which in turn is associated with consequences such as disability, disuse and depression.^{129–131} Thereby a vicious cycle arises that does not allow injured athletes to recover and adapt to their situation in an effective way.^{130,131} This indeed highlights the need to implement psychosocial aspects during sports rehabilitation. Taking into account that psychosocial factors, cognitive styles and personality traits influence certain pain modulatory systems through a complex collaboration of brain areas, this again indicates a possible target for modern pain neurosciences.

All together, we can conclude that modern pain neuroscience could be incorporated in sports science and sports medicine, especially in overuse injuries and tendinopathy. However, the use of pain neuroscience education has however not yet been studied in athletes.

Final comments

To date, the implementation of modern pain neuroscience has been generally limited to the field of manual (or musculoskeletal) therapy. Still, evidence for altered, but reversible pain processing (central sensitization) as underlying mechanism in post-cancer, paediatric and sports-related pain problems is increasing. Therefore, this masterclass article provides a rationale for the application of modern pain neurosciences within these pain populations. Although the general hypothesis states that modern pain neuroscience should be implemented within these three patient populations, research still needs to validate these ideas.

A therapy target for all chronic pain patients should comprise learning the patients how to cope with their pain. Although the three populations discussed in this masterclass are all very different, coping mechanisms emerge as key factor in all of them. Increasing the knowledge on pain neurosciences could decrease the perceived threat of pain and could therefore lead to more active and adaptive coping mechanisms and better pain tolerance.⁹⁷ Additionally, pain neuroscience education can play a very important role in redefining pain by positively changing pain beliefs, fears and other psychosocial factors, which is essential for the improvement of health status, behavioural responses and the successful return to physical activity.^{38,66,120} Given the evidence for the importance of physical activity and exercises in the management of the pain populations presented here, pain neuroscience education should become a part of therapy.^{81,82,98,99,102}

Another mutual and perpetuating factor in the three populations discussed here comprises an inadequate stress response. Not only post-cancer pain patients, but also paediatric patients and athletes also may suffer from an inadequate stress response (e.g., post-traumatic stress, stress due to medical interventions, stress to perform, etc.).^{132,133} Therefore, these patients might also benefit from implementing stress management within the rehabilitation programme, although this hypothesis should be validated by future research.

To end, rather than a diagnosis-based classification, we would like to advocate the use of a mechanism-based classification of pain types, which may better explain the variability and complexity of central pain problems. As patients suffering from the same dominant pain problem may benefit from the same type of treatment, this pain mechanism-based approach could lead to more patient-centred care, by recognizing the unique personal experience of pain (e.g., neurophysiological base of pain, but also pain beliefs, pain cognitions, emotions etc.).

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Conflicts of interest

The authors declare no conflicts of interest.

References

- Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol*. 2007;26(4):465–473.
- Nijs J, Torres-Cueco R, van Wilgen CP, et al. Applying modern pain neuroscience in clinical practice: criteria for the classification of central sensitization pain. *Pain Physician*. 2014;17(5):447–457.
- Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10(9):895–926.
- Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152:S2–S15.
- Meeus M, Nijs J, Van de Wauwer N, Toeback L, Truijzen S. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: an experimental study. *Pain*. 2008;139(2):439–448.
- Vierck CJJ. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). *Pain*. 2006;124(3):242–263.
- Giesecke T, Gracely RH, Grant MAB, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum*. 2004;50(2):613–623.
- Roussel NA, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp R. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clin J Pain*. 2013;29(7):625–638.
- de Tommaso M, Federici A, Franco G, et al. Suggestion and pain in migraine: a study by laser evoked potentials. *CNS Neurol Disord Drug Targets*. 2012;11(2):110–126.
- Farmer MA, Chanda ML, Parks EL, Baliki MN, Apkarian AV, Schaeffer AJ. Brain functional and anatomical changes in chronic prostatitis/chronic pelvic pain syndrome. *J Urol*. 2011;186(1):117–124.
- Yang CC, Lee JC, Kromm BG, Ciol MA, Berger RE. Pain sensitization in male chronic pelvic pain syndrome: why are symptoms so difficult to treat? *J Urol*. 2003;170(3):823–827.
- Fernandez-Carnero J, Fernandez-de-Las-Penas C, de la Llave-Rincon AI, Ge H-Y, Arendt-Nielsen L. Widespread mechanical pain hypersensitivity as sign of central sensitization in unilateral epicondylalgia: a blinded, controlled study. *Clin J Pain*. 2009;25(7):555–561.
- Paul TM, Soo Hoo J, Chae J, Wilson RD. Central hypersensitivity in patients with subacromial impingement syndrome. *Arch Phys Med Rehabil*. 2012;93(12):2206–2209.
- Fernandez-Lao C, Cantarero-Villanueva I, Fernandez-de-las-Penas C, Del-Moral-Avila R, Menjon-Beltran S, Arroyo-Morales M. Widespread mechanical pain hypersensitivity as a sign of central sensitization after breast cancer surgery: comparison between mastectomy and lumpectomy. *Pain Med*. 2011;12(1):72–78.
- Meeus M, Vervisch S, De Clerck LS, Moorkens G, Hans G, Nijs J. Central sensitization in patients with rheumatoid arthritis: a systematic literature review. *Semin Arthritis Rheum*. 2012;41(4):556–567.
- Staud R. Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. *Curr Rheumatol Rep*. 2002;4(4):299–305.
- Baranauskas G, Nistri A. Sensitization of pain pathways in the spinal cord: cellular mechanisms. *Prog Neurobiol*. 1998;54(3):349–365.
- Kwon M, Altin M, Duenas H, Alev L. The role of descending inhibitory pathways on chronic pain modulation and clinical implications. *Pain Pract*. 2014;14(7):656–667.
- Vachon-Presseau E, Centeno MV, Ren W, et al. The emotional brain as a predictor and amplifier of chronic pain. *J Dent Res*. 2016;95(6):605–612.
- Millan MJ. Descending control of pain. *Prog Neurobiol*. 2002;66(6):355–474.
- Apkarian AV, Sosa Y, Sonty S, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci*. 2004;24(46):10410–10415.
- Foerster BR, Petrou M, Edden RAE, et al. Reduced insular gamma-aminobutyric acid in fibromyalgia. *Arthritis Rheum*. 2012;64(2):579–583.
- Ichesco E, Schmidt-Wilcke T, Bhavsar R, et al. Altered resting state connectivity of the insular cortex in individuals with fibromyalgia. *J Pain*. 2014;15(8):815–826, e1.

24. Lieberman G, Shpaner M, Watts R, et al. White matter involvement in chronic musculoskeletal pain. *J Pain*. 2014;15(11):1110–1119.
25. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain*. 2005;9(4):463–484.
26. Gwilym SE, Filippini N, Douaud G, Carr AJ, Tracey I. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based morphometric study. *Arthritis Rheum*. 2010;62(10):2930–2940.
27. Seminowicz DA, Shpaner M, Keaser ML, et al. Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain. *J Pain*. 2013;14(12):1573–1584.
28. Shpaner M, Kelly C, Lieberman G, et al. Unlearning chronic pain: a randomized controlled trial to investigate changes in intrinsic brain connectivity following Cognitive Behavioral Therapy. *Neuroimage-Clin*. 2014;5:365–376.
29. Diers M, Yilmaz P, Rance M, et al. Treatment-related changes in brain activation in patients with fibromyalgia syndrome. *Exp Brain Res*. 2012;218(4):619–628.
30. Erpelding N, Simons L, Lebel A, et al. Rapid treatment-induced brain changes in pediatric CRPS. *Brain Struct Funct*. 2016;221(2):1095–1111.
31. Coombes BK, Bisset L, Vicenzino B. Thermal hyperalgesia distinguishes those with severe pain and disability in unilateral lateral epicondylalgia. *Clin J Pain*. 2012;28(7):595–601.
32. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. *Pain*. 2003;104(3):509–517.
33. Jull G, Sterling M, Kenardy J, Beller E. Does the presence of sensory hypersensitivity influence outcomes of physical rehabilitation for chronic whiplash? A preliminary RCT. *Pain*. 2007;129(1–2):28–34.
34. Moseley L. Combined physiotherapy and education is efficacious for chronic low back pain. *Aust J Physiother*. 2002;48(4):297–302.
35. Butler D, Moseley GL. *Explain Pain*. Adelaide: NOI Group Publishing; 2003.
36. Moseley GL, Butler DS. Fifteen years of explaining pain: the past, present, and future. *J Pain*. 2015;16(9):807–813.
37. Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijzen S. Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared with pacing and self-management education: a double-blind randomized controlled trial. *Arch Phys Med Rehabil*. 2010;91(8):1153–1159.
38. Louw A, Diener I, Butler DS, Puentedura EJ. The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. *Arch Phys Med Rehabil*. 2011;92(12):2041–2056.
39. Louw A, Diener I, Landers MR, Puentedura EJ. Preoperative pain neuroscience education for lumbar radiculopathy: a multicenter randomized controlled trial with 1-year follow-up. *Spine (Phila Pa 1976)*. 2014;39(18):1449–1457.
40. Clarke CL, Ryan CG, Martin DJ. Pain neurophysiology education for the management of individuals with chronic low back pain: systematic review and meta-analysis. *Man Ther*. 2011;16(6):544–549.
41. Van Oosterwijck J, Meeus M, Paul L, et al. Pain physiology education improves health status and endogenous pain inhibition in fibromyalgia: a double-blind randomized controlled trial. *Clin J Pain*. 2013;29(10):873–882.
42. Van Oosterwijck J, Nijs J, Meeus M, et al. Pain neurophysiology education improves cognitions, pain thresholds, and movement performance in people with chronic whiplash: a pilot study. *J Rehabil Res Dev*. 2011;48(1):43–58.
43. Moseley GL. Joining forces – combining cognition-targeted motor control training with group or individual pain physiology education: a successful treatment for chronic low back pain. *J Man Manip Ther*. 2003;11(2):88–94.
44. Duarte MA, Goulart EM, Penna FJ. Pressure pain threshold in children with recurrent abdominal pain. *J Pediatr Gastroenterol Nutr*. 2000;31(3):280–285.
45. Hermann C, Zohsel K, Hohmeister J, Flor H. Cortical correlates of an attentional bias to painful and innocuous somatic stimuli in children with recurrent abdominal pain. *Pain*. 2008;136(3):397–406.
46. Cornelissen L, Donado C, Kim J, et al. Pain hypersensitivity in juvenile idiopathic arthritis: a quantitative sensory testing study. *Pediatr Rheumatol Online J*. 2014;12:39.
47. Alfvén G. The covariation of common psychosomatic symptoms among children from socio-economically differing residential areas. An epidemiological study. *Acta Paediatr*. 1993;82(5):484–487.
48. Hogeweg JA, Kuis W, Oostendorp RA, Helders PJ. General and segmental reduced pain thresholds in juvenile chronic arthritis. *Pain*. 1995;62(1):11–17.
49. Hogeweg JA, Kuis W, Huygen AC, et al. The pain threshold in juvenile chronic arthritis. *Br J Rheumatol*. 1995;34(1):61–67.
50. Leegaard A, Lomholt JJ, Thastum M, Herlin T. Decreased pain threshold in juvenile idiopathic arthritis: a cross-sectional study. *J Rheumatol*. 2013;40(7):1212–1217.
51. Zohsel K, Hohmeister J, Flor H, Hermann C. Altered pain processing in children with migraine: an evoked potential study. *Eur J Pain*. 2008;12(8):1090–1101.
52. Reid GJ, Lang BA, McGrath PJ. Primary juvenile fibromyalgia: psychological adjustment, family functioning, coping, and functional disability. *Arthritis Rheum*. 1997;40(4):752–760.
53. Plinsinga ML, Brink MS, Vicenzino B, van Wilgen CP. Evidence of nervous system sensitization in commonly presenting and persistent painful tendinopathies: a systematic review. *J Orthop Sports Phys Ther*. 2015;45(11):864–875.
54. Harrington S, Gilchrist L, Sander A. Breast cancer EDGE task force outcomes: clinical measures of pain. *Rehabil Oncol (American Phys Ther Assoc Oncol Sect)*. 2014;32(1):13–21.
55. Ventafridda V, Caraceni A. Cancer pain classification: a controversial issue. Vol. 46, *Pain*. United States; 1991. p. 1–2.
56. Kumar SP, Saha S. Mechanism-based classification of pain for physical therapy management in palliative care: a clinical commentary. *Indian J Palliat Care*. 2011;17(1):80–86.
57. Smart KM, Blake C, Staines A, Thacker M, Doody C. Mechanisms-based classifications of musculoskeletal pain: part 1 of 3: symptoms and signs of central sensitisation in patients with low back (+/– leg) pain. *Man Ther*. 2012;17(4):336–344.
58. Nijs J, Apeldoorn A, Hallegraef H, et al. Low back pain: Guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. *Pain Physician*. 2015;18(3).
59. Kumar SP, Prasad K, Kumar VK, Shenoy K, Sisodia V. Mechanism-based classification and physical therapy management of persons with cancer pain: a prospective case series. *Indian J Palliat Care*. 2013;19(1):27–33.
60. Kumar SP. Cancer pain: a critical review of mechanism-based classification and physical therapy management in palliative care. *Indian J Palliat Care*. 2011;17(2):116–126.
61. Nijs J, Leysen L, Adriaenssens N, et al. Pain following cancer treatment: guidelines for the clinical classification of predominant neuropathic, nociceptive and central sensitization pain. *Acta Oncol*. 2016;55(6):659–663.
62. Fainsinger RL, Nekolaichuk CL, Lawlor PG, Neumann CM, Hanson J, Vigano A. A multicenter study of the revised Edmonton Staging System for classifying cancer pain in advanced cancer patients. *J Pain Symptom Manage*. 2005;29(3):224–237.

63. Knudsen AK, Aass N, Fainsinger R, et al. Classification of pain in cancer patients – a systematic literature review. *Palliat Med.* 2009;23(4):295–308.
64. Bennett MI, Bagnall A-M, Jose Closs S. How effective are patient-based educational interventions in the management of cancer pain? Systematic review and meta-analysis. *Pain.* 2009;143(3):192–199.
65. Nijs J, Paul van Wilgen C, Van Oosterwijck J, van Ittersum M, Meeus M. How to explain central sensitization to patients with “unexplained” chronic musculoskeletal pain: practice guidelines. *Man Ther.* 2011;16(5):413–418.
66. Moseley GL. Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. *Eur J Pain.* 2004;8(1):39–45.
67. Khasar SG, Burkham J, Dina OA, et al. Stress induces a switch of intracellular signaling in sensory neurons in a model of generalized pain. *J Neurosci.* 2008;28(22):5721–5730.
68. Quintero L, Cuesta MC, Silva JA, et al. Repeated swim stress increases pain-induced expression of c-Fos in the rat lumbar cord. *Brain Res.* 2003;965(1–2):259–268.
69. Quintero L, Cardenas R, Suarez-Roca H. Stress-induced hyperalgesia is associated with a reduced and delayed GABA inhibitory control that enhances post-synaptic NMDA receptor activation in the spinal cord. *Pain.* 2011;152(8):1909–1922.
70. Quintero L, Moreno M, Avila C, Arcaya J, Maixner W, Suarez-Roca H. Long-lasting delayed hyperalgesia after sub-chronic swim stress. *Pharmacol Biochem Behav.* 2000;67(3):449–458.
71. McLean SA, Clauw DJ, Abelson JL, Liberzon I. The development of persistent pain and psychological morbidity after motor vehicle collision: integrating the potential role of stress response systems into a biopsychosocial model. *Psychosom Med.* 2005;67(5):783–790.
72. Martenson ME, Cetas JS, Heinricher MM. A possible neural basis for stress-induced hyperalgesia. *Pain.* 2009;142(3):236–244.
73. Suarez-Roca H, Leal L, Silva JA, Pinerua-Shuhaibar L, Quintero L. Reduced GABA neurotransmission underlies hyperalgesia induced by repeated forced swimming stress. *Behav Brain Res.* 2008;189(1):159–169.
74. Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. *Psychosom Med.* 2005;67(2):277–280.
75. Porter LS, Mishel M, Neelon V, Belyea M, Pisano E, Soo MS. Cortisol levels and responses to mammography screening in breast cancer survivors: a pilot study. *Psychosom Med.* 2003;65(5):842–848.
76. Bower JE, Ganz PA, Dickerson SS, Petersen L, Aziz N, Fahey JL. Diurnal cortisol rhythm and fatigue in breast cancer survivors. *Psychoneuroendocrinology.* 2005;30(1):92–100.
77. Crosswell AD, Lockwood KG, Ganz PA, Bower JE. Low heart rate variability and cancer-related fatigue in breast cancer survivors. *Psychoneuroendocrinology.* 2014;45:58–66.
78. Caro-Moran E, Fernandez-Lao C, Galiano-Castillo N, Cantarero-Villanueva I, Arroyo-Morales M, Diaz-Rodriguez L. Heart rate variability in breast cancer survivors after the first year of treatments: a case-controlled study. *Biol Res Nurs.* 2016;18(1):43–49.
79. Phillips KM, Antoni MH, Lechner SC, et al. Stress management intervention reduces serum cortisol and increases relaxation during treatment for nonmetastatic breast cancer. *Psychosom Med.* 2008;70(9):1044–1049.
80. Stagl JM, Bouchard LC, Lechner SC, et al. Long-term psychological benefits of cognitive-behavioral stress management for women with breast cancer: 11-year follow-up of a randomized controlled trial. *Cancer.* 2015;121(11):1873–1881.
81. Irwin ML, Cartmel B, Gross CP, et al. Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *J Clin Oncol.* 2015;33(10):1104–1111.
82. Mishra SI, Scherer RW, Geigle PM, et al. Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev.* 2012;(8):CD007566.
83. Cantarero-Villanueva I, Fernández-Lao C, Fernández-de-Las-Peñas C, et al. Effectiveness of water physical therapy on pain, pressure pain sensitivity, and myofascial trigger points in breast cancer survivors: a randomized, controlled clinical trial. *Pain Med.* 2012;13(11):1509–1519.
84. Cantarero-Villanueva I, Fernandez-Lao C, Caro-Moran E, et al. Aquatic exercise in a chest-high pool for hormone therapy-induced arthralgia in breast cancer survivors: a pragmatic controlled trial. *Clin Rehabil.* 2013;27(2):123–132.
85. Nijs J, Meeus M, Cagnie B, et al. A modern neuroscience approach to chronic spinal pain: combining pain neuroscience education with cognition-targeted motor control training. *Phys Ther.* 2014;94(5):730–738.
86. Nijs J, Lluch Girbes E, Lundberg M, Malfliet A, Sterling M. Exercise therapy for chronic musculoskeletal pain: innovation by altering pain memories. *Man Ther.* 2015;20(1):216–220.
87. Simons LE, Basch MC. State of the art in biobehavioral approaches to the management of chronic pain in childhood. *Pain Manag.* 2016;6(1):49–61.
88. King S, Chambers CT, Huguet A, et al. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. *Pain.* 2011;152(12):2729–2738.
89. Palermo TM, Chambers CT. Parent and family factors in pediatric chronic pain and disability: an integrative approach. *Pain.* 2005;119(1–3):1–4.
90. Korterink JJ, Diederik K, Benninga MA, Tabbers MM. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. *PLoS One.* 2015;10(5):e0126982.
91. Roth-Isigkeit A, Thyen U, Stoven H, Schwarzenberger J, Schmucker P. Pain among children and adolescents: restrictions in daily living and triggering factors. *Pediatrics.* 2005;115(2):e152–e162.
92. Vervoort T, Logan DE, Goubert L, De Clercq B, Hublet A. Severity of pediatric pain in relation to school-related functioning and teacher support: an epidemiological study among school-aged children and adolescents. *Pain.* 2014;155(6):1118–1127.
93. Walker LS, Dengler-Crisch CM, Rippel S, Bruehl S. Functional abdominal pain in childhood and adolescence increases risk for chronic pain in adulthood. *Pain.* 2010;150(3):568–572.
94. von Baeyer CL, Marche TA, Rocha EM, Salmon K. Children’s memory for pain: overview and implications for practice. *J Pain.* 2004;5(5):241–249.
95. Landry BW, Fischer PR, Driscoll SW, et al. Managing chronic pain in children and adolescents: a clinical review. *PM R.* 2015;7:S295–S315.
96. Eccleston C, Palermo TM, Williams AC de C, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. *Cochrane Database Syst Rev.* 2014;5(5):CD003968.
97. Jackson T, Pope L, Nagasaka T, Fritch A, Iezzi T, Chen H. The impact of threatening information about pain on coping and pain tolerance. *Br J Health Psychol.* 2005;10:441–451.
98. Sherry DD, Wallace CA, Kelley C, Kidder M, Sapp L. Short- and long-term outcomes of children with complex regional pain syndrome type I treated with exercise therapy. *Clin J Pain.* 1999;15(3):218–223.
99. Clinch J, Eccleston C. Chronic musculoskeletal pain in children: assessment and management. *Rheumatology.* 2009;48(5):466–474.
100. Michaleff ZA, Kamper SJ, Maher CG, Evans R, Broderick C, Henschke N. Low back pain in children and adolescents: a systematic review and meta-analysis evaluating the

- effectiveness of conservative interventions. *Eur Spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc.* 2014;23(10):2046–2058.
101. Palmer S, Bailey S, Barker L, Barney L, Elliott A. The effectiveness of therapeutic exercise for joint hypermobility syndrome: a systematic review. *Physiotherapy.* 2014;100(3):220–227.
 102. Kimura Y, Walco GA. Pain in children with rheumatic diseases. *Curr Rheumatol Rep.* 2006;8(6):480–488.
 103. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports.* 2006;16(Suppl. 1):3–63.
 104. Donaldson SJ, Ronan KR. The effects of sports participation on young adolescents' emotional well-being. *Adolescence.* 2006;41(162):369–389.
 105. Meeuwisse WH, Tyreman H, Hagel B, Emery C. A dynamic model of etiology in sport injury: the recursive nature of risk and causation. *Clin J Sport Med Off J Can Acad Sport Med.* 2007;17(3):215–219.
 106. Maffey L, Emery C. What are the risk factors for groin strain injury in sport? A systematic review of the literature. *Sports Med.* 2007;37(10):881–894.
 107. Tyler TF, Mullaney MJ, Mirabella MR, Nicholas SJ, McHugh MP. Risk factors for shoulder and elbow injuries in high school baseball pitchers: the role of preseason strength and range of motion. *Am J Sports Med.* 2014;42(8):1993–1999.
 108. Witvrouw E, Lysens R, Bellemans J, Cambier D, Vanderstraeten G. Intrinsic risk factors for the development of anterior knee pain in an athletic population. A two-year prospective study. *Am J Sports Med.* 2000;28(4):480–489.
 109. Walker H, Gabbe B, Wajswelner H, Blanch P, Bennell K. Shoulder pain in swimmers: a 12-month prospective cohort study of incidence and risk factors. *Phys Ther Sport.* 2012;13(4):243–249.
 110. van Wilgen CP, Keizer D. Neuropathic pain mechanisms in patients with chronic sports injuries: a diagnostic model useful in sports medicine? *Pain Med.* 2011;12(1):110–117.
 111. Bahr R. No injuries, but plenty of pain? On the methodology for recording overuse symptoms in sports. *Br J Sports Med.* 2009;43(13):966–972.
 112. Skinner IW, Debenham JR, Krumenachera S, Bulsarab MK, Wand BM. Chronic mid portion Achilles tendinopathy is not associated with central sensitisation. *Pain Rehabil J Physiother Pain Assoc.* 2014;2014(37):34–40.
 113. Tompra N, van Dieen JH, Coppieters MW. Central pain processing is altered in people with Achilles tendinopathy. *Br J Sports Med.* 2016;50(16):1004–1007.
 114. van Wilgen CP, Konopka KH, Keizer D, Zwerver J, Dekker R. Do patients with chronic patellar tendinopathy have an altered somatosensory profile? A Quantitative Sensory Testing (QST) study. *Scand J Med Sci Sports.* 2013;23(2):149–155.
 115. Debenham J, Butler P, Mallows A, Wand BM. Disrupted tactile acuity in people with achilles tendinopathy: a preliminary case-control investigation. *J Orthop Sports Phys Ther.* 2016;46(12):1061–1064.
 116. Junge A. The influence of psychological factors on sports injuries. Review of the literature. *Am J Sports Med.* 2000;28:S10–S15.
 117. Mallows A, Debenham J, Walker T, Littlewood C. Association of psychological variables and outcome in tendinopathy: a systematic review. *Br J Sports Med.* 2016. Epub ahead of print.
 118. van Wilgen CP, Verhagen EALM. A qualitative study on overuse injuries: the beliefs of athletes and coaches. *J Sci Med Sport.* 2012;15(2):116–121.
 119. Shrier I, Matheson GO, Boudier-Reveret M, Steele RJ. Validating the three-step return-to-play decision model. *Scand J Med Sci Sports.* 2015;25(2):e231–e239.
 120. Creighton DW, Shrier I, Shultz R, Meeuwisse WH, Matheson GO. Return-to-play in sport: a decision-based model. *Clin J Sport Med Off J Can Acad Sport Med.* 2010;20(5):379–385.
 121. Ardern CL, Taylor NF, Feller JA, Whitehead TS, Webster KE. Psychological responses matter in returning to preinjury level of sport after anterior cruciate ligament reconstruction surgery. *Am J Sports Med.* 2013;41(7):1549–1558.
 122. Ardern CL, Taylor NF, Feller JA, Webster KE. Fear of re-injury in people who have returned to sport following anterior cruciate ligament reconstruction surgery. *J Sci Med Sport.* 2012;15(6):488–495.
 123. Tripp DA, Stanish WD, Reardon G, Coady C, Sullivan MJL. Comparing postoperative pain experiences of the adolescent and adult athlete after anterior cruciate ligament surgery. *J Athl Train.* 2003;38(2):154–157.
 124. Tripp DA, Stanish W, Ebel-Lam A, Brewer B. Fear of reinjury, negative affect, and catastrophizing predicting return to sport in recreational athletes with anterior cruciate ligament injuries at 1 year postsurgery. *Rehabil Psychol.* 2007;52(1):73–81.
 125. Baranoff J, Hanrahan SJ, Connor JP. The roles of acceptance and catastrophizing in rehabilitation following anterior cruciate ligament reconstruction. *J Sci Med Sport.* 2015;18(3):250–254.
 126. Kvist J, Ek A, Sporrstedt K, Good L. Fear of re-injury: a hindrance for returning to sports after anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc.* 2005;13(5):393–397.
 127. Devgan A, Magu NK, Siwach RC, Rohilla R, Sangwan SS. Functional outcome in athletes at five years of arthroscopic anterior cruciate ligament reconstruction. *ISRN Orthop.* 2011:570329.
 128. McCullough KA, Phelps KD, Spindler KP, et al. Return to high school- and college-level football after anterior cruciate ligament reconstruction: a Multicenter Orthopaedic Outcomes Network (MOON) cohort study. *Am J Sports Med.* 2012;40(11):2523–2529.
 129. George SZ, Stryker SE. Fear-avoidance beliefs and clinical outcomes for patients seeking outpatient physical therapy for musculoskeletal pain conditions. *J Orthop Sports Phys Ther.* 2011;41(4):249–259.
 130. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain.* 2000;85(3):317–332.
 131. Leeuw M, Goossens MEJB, Linton SJ, Crombez G, Boersma K, Vlaeyen JWS. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med.* 2007;30(1):77–94.
 132. Heidari J, Mierswa T, Kleinert J, et al. Parameters of low back pain chronicity among athletes: associations with physical and mental stress. *Phys Ther Sport.* 2016;21:31–37.
 133. Noel M, Wilson AC, Holley AL, Durkin L, Patton M, Palermo TM. Posttraumatic stress disorder symptoms in youth with vs without chronic pain. *Pain.* 2016;157(10):2277–2284.