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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 syndrome[5] 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 pain[14] 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 pain[2] 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.

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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 superior outcome. In 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 rhythms[76] 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 of 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. However, 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

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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 pain[101] 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 to 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-analyses signs of central sensitization were found in upper-limb tendinopathies[53] 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.

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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 review are all very different, coping mechanisms emerge as key factor in all of them. Increasing the knowledge on pain neurosciences could decrease the perceived thread 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

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