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RECONCEPTUALISING PAIN ACCORDING TO MODERN PAIN SCIENCE

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This paper argues that the biology of pain is never really straightforward, even when it appears to be. It is proposed that understanding what is currently known about the biology of pain requires a reconceptualisation of what pain actually is, and how it serves our livelihood. There are four key points: (i) that pain does not provide a measure of the state of the tissues; (ii) that pain is modulated by many factors from across somatic, psychological and social domains; (iii) that the relationship between pain and the state of the tissues becomes less predictable as pain persists; and (iv) that pain can be conceptualised as a conscious correlate of the implicit perception that tissue is in danger. These issues raise conceptual and clinical implications, which are discussed with particular relevance to persistent pain. Finally, this conceptualisation is used as a framework for one approach to understanding complex regional pain syndrome.

Keywords: Pain, re-evaluation, persistent pain, pain syndrome

INTRODUCTION

At first glance, pain seems relatively straightforward – hitting one's thumb with a hammer hurts one's thumb. Such experiences are easily understood with a structural-pathology model, which supposes pain provides an accurate indication of the state of the tissues. However, on closer inspection, pain is less straightforward. Much of the pain we see clinically fits into this less straightforward category, where pain cannot be understood as a marker of the state of the tissues. This paper argues that the biology of pain is never really straightforward, even when it appears to be. There are four key points: (i) that pain does not provide a measure of the state of the tissues; (ii) that pain is modulated by many factors from across somatic, psychological and social domains; (iii) that the relationship between pain and the state of the tissues becomes less predictable as pain persists; and (iv) that pain can be conceptualised as a conscious correlate of the implicit perception that tissue is in danger. These points will be discussed in light of their clinical implications and will form the basis of one approach to understanding complex regional pain syndrome.

Pain does not provide a measure of the state of the tissues

In 1965, the gate control theory[2] was proposed to explain the variable response of animals to noxious stimuli. The theory proposed that noxious input was modulated at the spinal cord by other non-noxious input from the periphery, and by descending input from higher centres. That theory was interrogated in many animal experiments (see Wall and McMahon[3] for a review). A typical experiment would involve the insertion of recording electrodes into the nociceptors of the study animal, applying a defined injury and recording nociceptor activity. Finally, experimenters would record behaviours of the animal that implied that the animal was in pain. These behaviours might be relatively simple; for example, the reaction time of a withdrawal reflex. They might be relatively complex;

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for example, the ratio between time spent in a non-preferred environment (*e.g.* illuminated box) with a cool floor, and time spent in a preferred environment (*e.g.* dark box) with a heated floor.[4]

Two findings consistently emerged from those studies. First, the injury, or noxious stimulation, initiates the change in behaviour. Second, neither pain behaviour nor nociceptor activity hold an isomorphic relationship with the state of the tissues. By clearly demonstrating these things, those studies provided the first experimental evidence that pain does not provide a measure of the state of the tissues.

One limitation of animal experiments is that they do not tell us about pain. Human experiments, however, can. Although it is difficult to justify injuring human volunteers, it is possible to deliver non-harmful noxious stimuli, for example brief thermal, electrical or mechanical stimuli (see Handwerker and Kobal[5] for a review of various methods of experimentally inducing pain). By recording activity in nociceptors while simultaneously recording subjects' pain ratings, experimenters have been able to evaluate the relationship between the state of the tissues (in the absence of tissue damage), activity in nociceptors, and pain.[6]

Human pain experiments corroborated both findings from the animal data. Specifically, noxious stimulation is necessary for nociceptor activity, which usually reflects the intensity of the stimulus, and nociceptor activation does not provide an accurate measure of the state of the tissues.[6] The human experiments went further because they showed that the relationship between pain ratings and nociceptor activation is variable. In fact, some authors have proposed that the notion of nociceptors is misleading because small diameter fibres (Aδ and C fibres) respond to very small (non-harmful) changes in the internal state of the body.[7] That said, some small diameter fibres are not responsive to small changes (so-called high-threshold neurons) and this sub-class of small diameter fibres may reflect what we call nociceptors. Regardless, it is clear that experimental studies do not show an isomorphic relationship between pain and nociceptor activity, nor between pain and the state of the tissues. Rather, they show a variable relationship that is modulated by many factors.

Pain is modulated by many factors from across somatic, psychological and social domains

Anecdotal evidence that somatic, psychological and social factors modulate pain is substantial – sport-related and war-related stories are common (see Butler and Moseley[8] for several examples). However, numerous experimental findings corroborate the anecdotal evidence (see Fields *et al.*[9] for a review of central nervous system mechanisms of modulation). Other factors that are known to modulate the pain evoked by a standardised stimulus include inflammatory mediators (increase nociceptor activity), tissue temperature (increased temperature increases nociceptor activity via summation), and blood flow (decreased blood flow increases nociceptor activity via summation induced by H^+ ions). See Meyer *et al.*[6] for a review of peripheral mechanisms of modulation.

Experiments that manipulate the psychological context of a noxious stimulus often demonstrate clear effects on pain, although the direction of these effects is not always consistent. For example, a large amount of literature concerns the effect of attention on pain, and of pain on attention.[10–22] Despite the wealth of data, consensus is lacking: some data suggest that attending to pain amplifies it and attending away from pain nullifies it, but others suggest the opposite.

Anxiety also seems to have variable effects on pain. Some reports link increased anxiety to increased pain during clinical procedures[23–26] and during experimentally induced pain,[27] but other reports suggest no effect.[28,29] Relevant reviews conclude that the influence of anxiety on pain is probably largely dependent on attention.[28,30]

Expectation also seems to have variable effects on pain. As a general rule, expectation of a noxious stimulus increases pain if the cue signals a more intense or more damaging stimulus[22,31–35] and decreases pain if the cue signals a less intense or less damaging stimulus (see Fields[34] and Wager[36] for reviews). Further, cues that signal an impending decrease in pain, for example the process of taking an analgesic, usually decrease pain. Thus, expectation is thought to play a major role in placebo analgesia.[37,38]

The common denominator of the effect of attention, anxiety and expectation on pain seems to be the underlying evaluative context, or meaning of the pain. That is demonstrated by the consistent effect that some cognitive states seem to have on pain. For example, catastrophic interpretations of pain are associated with higher pain ratings in both clinical and experimental studies (see Sullivan *et al.*[39] for a review). Believing pain to be an accurate indicator of the state of the tissues is associated with higher pain ratings,[40] whereas believing that the nervous system amplifies noxious input in chronic pain states increases pain threshold during straight leg raise.[41]

The social context of a noxious stimulus also affects the pain it evokes. Initiation practices and sadomasochistic sexual practices are two examples that highlight the importance of social context. Overall, the effects of social context are again variable but again seem to be underpinned by the underlying evaluative context, or meaning (see Butler and Moseley[8] for a review of pain-related data

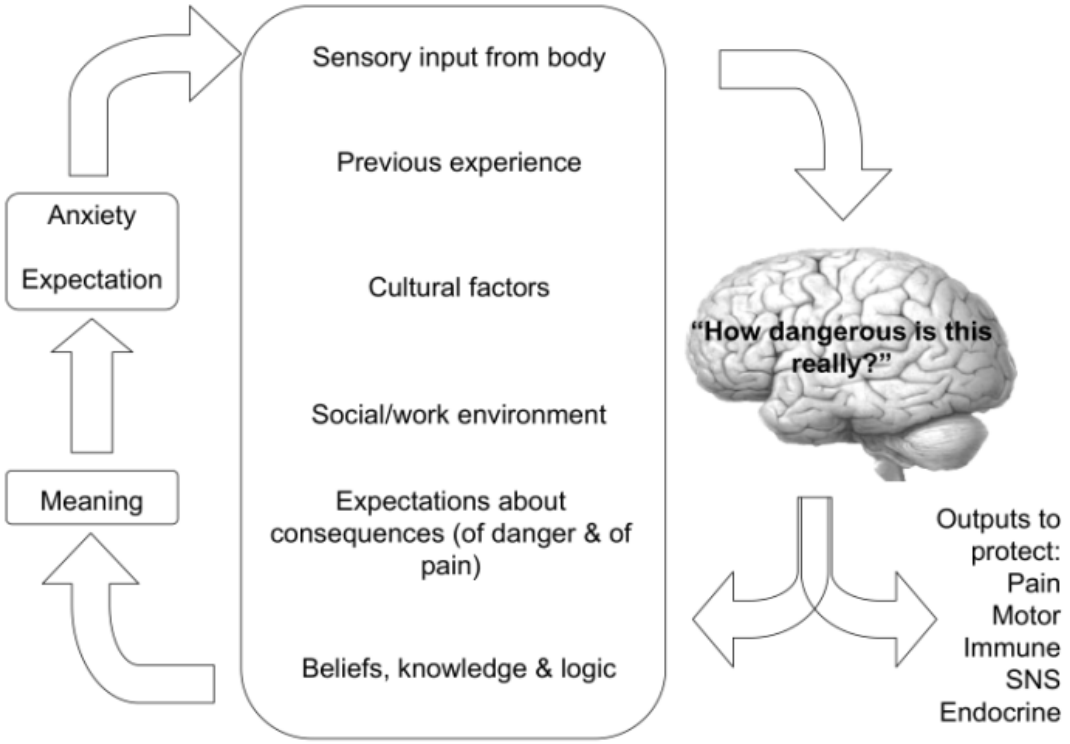

Fig. 1. Many inputs affect the implicit perception of threat to body tissues, labelled here as 'How dangerous is this really?' Those inputs have wider meaning effects, which in turn seems to affect anxiety, attention and expectation. The implicit perception of threat to body tissues determines pain and in turn influences other inputs.

and Moerman[42] for exhaustive coverage of the role of meaning in health and medicine).

To review the very large amount of literature on somatic, psychological and social influences on pain is beyond the scope of this paper. However, it is appropriate, and clinically meaningful, to reiterate the theme that emerges from that literature: that the influences are variable and seem to depend on the evaluative context of the noxious input.

The relationship between pain and the state of the tissues becomes weaker as pain persists

The nervous system is dynamic. This means that the functional properties of individual neurones and of synergies of neurones change in response to activity. To review all the changes that have been identified is beyond the scope of this paper and the expertise of this author. However, the nature of the changes can be summarised thus: that the neurones that transmit nociceptive input to the brain become sensitised as nociception persists, and that the networks of neurons within the brain that evoke pain, become sensitised as pain persists. The molecular and systems biology of these changes have been discussed at several levels.[8,43,44] The clinical manifestations of these changes are: hyperalgesia (formerly painful stimuli become more painful) and allodynia (formerly non-painful stimuli become painful). These terms are used widely, most often in reference to tactile stimuli, but also in reference to movement and to thermal stimuli.

One aspect of the changes that occur when pain persists is that the proprioceptive representation of the painful body part in primary sensory cortex changes.[45–47] This may have implications for motor control because these representations are the maps that the brain uses to plan and execute movement.[48] If the map of a body part becomes inaccurate, then motor control may be compromised – it is known that experimental disruption of cortical proprioceptive maps disrupts motor planning.[49] The notion of distorted proprioceptive representation has been discussed with regard to its impact on motor control[50,51] and, more recently, in a theoretical way with regard to pain.[52] Although exceptions exist,[53] there is mounting evidence that changes in cortical representation occur in association with chronic pain, and it is feasible that these changes may become part of the problem.[46]

Conceptualising pain as a conscious correlate of the implicit perception that tissue is in danger

The biology of pain is complex. One response to this complexity is to develop clinically viable conceptual

paradigms that incorporate what is now known about that complexity. One such paradigm that is gaining support is the neuromatrix theory (see Melzack[55] for a contextual review),[54] which conceptualises pain as one output of the central nervous system that occurs when the organism perceives tissue to be under threat. There are two important components of this conceptualisation. First, there are other central nervous system outputs that occur when tissue is perceived to be under threat, and second, that it is the implicit perception of threat that determines the outputs, not the state of the tissues, nor the actual threat to the tissues (Fig. 1).

When tissue is under threat, a range of local and segmental responses occur. For example, inflammatory mediators are released, the body part is usually withdrawn via short and long latency reflex loops, there are rapid changes in blood flow and in the excitability of peripheral nociceptors (so-called peripheral sensitisation).[56] The nociceptive system transforms this threat into electrical activity in peripheral neurones. If this message of threat is then transmitted by spinal neurones to higher centres, the responses become more complex. For example, immune mediators are released into the blood stream,[57] voluntary and postural muscle activity are altered[58] and conscious knowledge of the threat (*i.e.* pain) may emerge. Within this context, pain will not emerge until the nociceptive input to the brain has been evaluated, albeit at an unconscious level (see Moseley[59] and Gifford *et al.*[60] for further discussion).

The second important component of the neuromatrix theory is that pain depends on the perceived degree of threat. This means that pain can be conceptualised as the conscious correlate of the implicit perception of threat to body tissues.[8,59] That psychosocial factors are very important in most chronic pain states is well established.[61–65] This paper argues that the mass of data regarding psychosocial factors can be gathered within the proposed conceptualisation that pain is one output of the central nervous system that occurs when the organism perceives tissue to be under threat. The conceptualisation has limitations and strengths. One limitation is that it does not attempt to describe the biology of implicit evaluation of threat, nor of how this might emerge into consciousness. In this sense it adds little to theories first proposed decades ago (see, for example, Hebb[66]). However, a strength of this conceptualisation is that it can easily be integrated into a clinical context where making sense of the influence of factors from across somatic, psychological and social domains is valuable.

Implications for clinical practice

That pain does not reflect the state of the tissues, but rather is a conscious driver of behaviour aimed at protecting those tissues, has implications for clinical practice. One implication is that to base clinical reasoning on what is currently known about the biology of pain requires that the skills and knowledge of the clinician are broader than those related to anatomy and biomechanics. That is, the clinician must have a sound knowledge of diagnostic tools, tissue dynamics, healing and remodelling, peripheral and central sensitisation, and psychological and social factors that might affect the implicit perception of threat to body tissues. This information is readily available and there is evidence that clinicians can understand modern concepts with relatively limited training.[67] That said, it may be unrealistic to expect clinicians to keep up-to-date with progress in knowledge across these areas. This points to a strength of the conceptualisation of pain as the conscious correlate of the implicit perception threat to body tissues because the clinician can use the conceptual model to guide treatment. That is, rather than know and understand all the evidence about which somatic, psychological and social factors have been demonstrated to modulate pain, and the nature of their modulation, the clinician can consider each factor in terms of what effect it might have on the implicit perception of threat. This conceptual model seeks to synthesize that wide body of evidence into a principle.

Another implication that is worthy of special mention is that patients should be helped to base their reasoning, about their condition and their pain, on similar information. This is important because teaching patients about modern pain biology leads to altered beliefs and attitudes about pain[40] and increased pain thresholds during relevant tasks.[41] Moreover, when education about pain biology is incorporated into physiotherapy management of patients with chronic pain, pain and disability are reduced.[68,69] A key objective of such education is to encourage patients to apply the same principle as that advocated for clinicians, summarised here as 'what effect might this (factor) have on the implicit perception of threat', or in patient-appropriate language, 'how does this affect the answer to the question, how dangerous is this really?'.[8]

USING THIS CONCEPTUALISATION TO UNDERSTAND CRPS AND GUIDE NEW OPTIONS FOR MANAGEMENT

Complex regional pain syndrome (CRPS) is a debilitating condition that can occur after minor trauma, and sometimes without peripheral trauma, for example, post-stroke.[70] Much is known about the pathophysiology of CRPS, including facilitated neurogenic

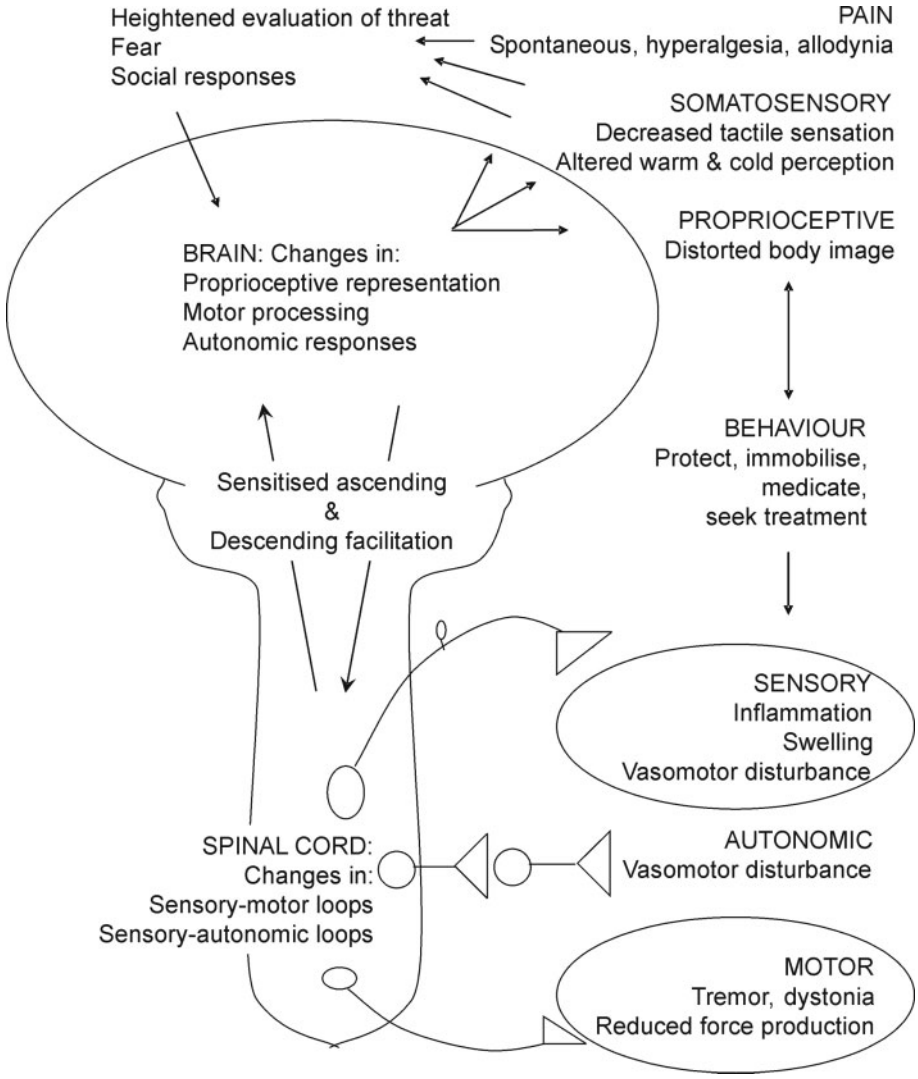

Fig. 2. Schematic overview of pathophysiology of complex regional pain syndrome. Adapted from Janig and Baron.[75]

inflammation[71,72] and tissue hypoxia[73] at the injury site,[74,75] autonomic,[76] immune,[77–79] motor,[80,81] tactile[82–85] and proprioceptive[86] dysfunction (Fig. 2).

The syndromic pattern of signs and symptoms includes pain, hyperalgesia, allodynia, dystonia, swelling, abnormal blood flow, abnormal sweating, hair and nail growth. The sensitivity to provocation can be remarkable, for example, elicitation of pain, swelling and (anecdotally) blood flow changes in response to imagined movements[87] or when the patient receives visual input that the limb is being touched, even though it is not in fact being touched ('dysynchiria').[88] The wide-spread and multisystemic nature of the pathophysiology of CRPS implies that, although CRPS is usually initiated by peripheral insult, it is a disorder of the central nervous system.[75]

When one tries to make sense of such a multisystemic and exaggerated response to minor injury, the conceptualisation that pain is a conscious correlate of the implicit perception of the threat to body tissue can be useful. That pain is just one output by which the brain might try to protect the tissues – one aspect of a homeostatic response[89] – lends itself to CRPS because the other responses are so patent. That pain is a correlate of implicitly perceived threat to body tissue, rather than the state of the tissues, or the actual threat to the tissues, is particularly relevant to CRPS in the absence of any tissue or neural injury, for example, as a stress response.[90]

Each of the pathological findings that have been documented in patients with CRPS might be considered a protective response, whether it be an immune, motor, sensory, vascular, autonomic or conscious response. consistent with attempts to protect the part in question, by utilising immune, motor, sensory, vascular and autonomic systems as well as consciousness. Reducing the threshold for activation of these protective responses would seem a particularly effective way to protect the body part in question, for example making it so sensitive that even looking at it being touched activates a protective response.[88]

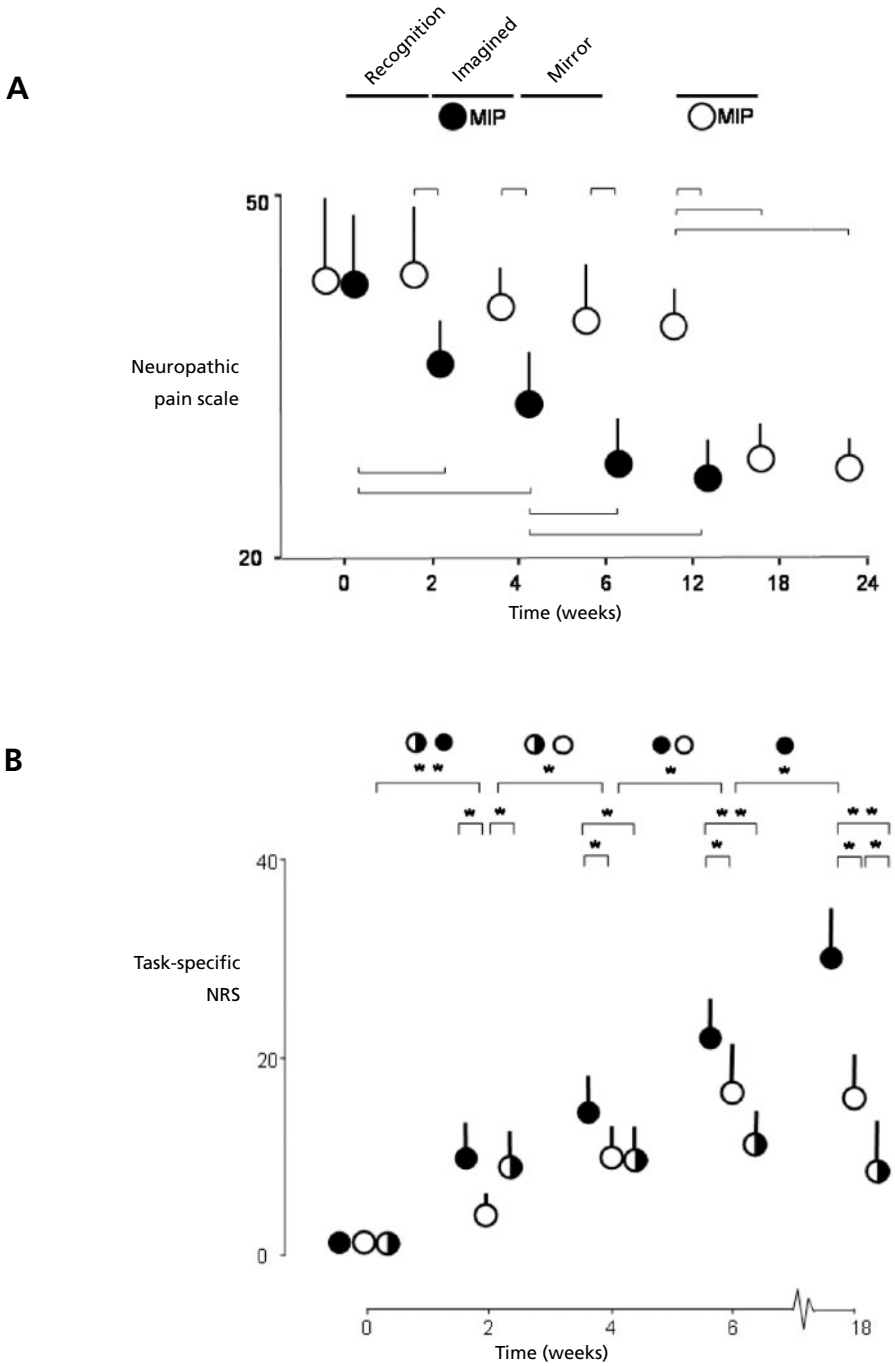

Fig. 3. Response to different components of motor imagery. Pain (A) and functional capacity (B): Recog = laterality recognition whereby patients make left/right judgements of pictured hands; Imag. = imagined movements; Mirror = mirror movements. Three groups are shown: group 1 undertook the motor imagery program, group 2 performed imagined movements first, then laterality recognition and then mirror movements, group 3 performed laterality recognition, followed by mirror movements and then back to laterality recognition. Note that group 1 had a largest reduction in pain. Note also, variable responses to imagined and mirror movements, depending on the order of components. From Moseley[1] and Moseley[93] with permission.

The challenge for those trying to understand CRPS according to this paradigm is to identify why the implicit perception of threat to body tissues is so exaggerated in some patients and in some situations, but not in others. Fundamental to the paradigm is that anything that modulates implicitly perceived threat should be relevant. That means that psychosocial factors, including anxiety, depression, attitudes and beliefs, social context or work status may all play an important role. Although patients with CRPS do not demonstrate a 'typical' psychosocial profile, psychosocial contributors are probably relevant in the majority of cases. Finally, there is initial evidence for a genetic contribution to CRPS,[91] but more data are required to clarify that possibility.

Clinical response to CRPS according to this paradigm

If CRPS is an exaggerated protective response, then it seems sensible to devise treatment that aims first to find a baseline that is sufficiently conservative to not elicit the unwanted protective responses (to 'get under the radar'), and second to expose the limb gradually to threat while continuing to avoid elicitation of the unwanted responses. This approach underpins graded motor imagery for CRPS,[92,93] whereby patients begin training by making left/right judgements of pictured limbs. It is known that this task activates cortical networks that involve representation of the limb and preparation for movement,[94] but this task does not activate primary sensory and motor cortices.[95] Graded motor imagery progresses from left/right laterality judgements to imagined movements, which do activate primary sensory and motor cortices,[95,96] and then to mirror movements. The order of these components seems to be important in the effect on pain and disability in patients with chronic CRPS (Fig. 3).[1] In patients with acute (or anecdotally less severe) CRPS, it may be sufficient to begin training (conceptualised here as exposure to threat) with mirror movements.[97]

One of the key issues outlined earlier is that the nervous system changes when nociception and pain persist. There is a large amount of evidence that the cortical representation of the affected limb undergoes substantial changes in patients with CRPS[47,74,75,83,98–100] and these changes have been implicated in the maintenance of pathological pain syndromes (although see Moseley[53] for a word of caution).[46] If distorted cortical representation contributes to CRPS, then it would seem sensible to attempt to normalise cortical representation of the limb. This has been done in patients with phantom limb pain,[101] which is associated with changes in primary sensory cortex that are probably similar to those observed in CRPS (see Acerra *et al.*[102] for a review of common findings in phantom limb pain, stroke and CRPS). In that study with amputees, sensory discrimination training evoked normalisation of cortical representation, improvement in tactile acuity on the stump and reduction/elimination of phantom limb pain.[101] Increase in tactile acuity, normalisation of cortical representation and reduction in pain were positively related.

Finally, if CRPS reflects an exaggerated implicit perception of threat to body tissue, then it would seem sensible to attempt to reduce the perception of threat. One approach that has been studied extensively in other populations is the explanation to the patient of the underlying biology of their pain. Preliminary data from patients with CRPS appear promising,[103] but clinical trials are required.

CONCLUSIONS

Extensive experimental data corroborate anecdotal evidence that pain does not provide a measure of the state of the tissues and that pain is modulated by many factors from across somatic, psychological and social domains. It is now known that as nociception and pain persist, the neuronal mechanisms involved in both become more sensitive, which means that the relationship between pain and the state of the tissues becomes weaker and less predictable. One paradigm, which considers the current thought in pain biology, conceptualises pain as the conscious correlate of the implicit perception of threat to body tissue. This conceptualisation can be applied clinically to identify factors from across somatic, psychological and social domains that may affect the perceived threat to tissue damage. Further, it suggests approaches to treatment that target those factors. Evidence from clinical trials suggests that clinical strategies based on this conceptualisation can be effective in patients with disabling complex and chronic pain.

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