Titolo rivista/libro: Nature reviews. Neurology (Online)

Titolo articolo/sezione:

Autore/i: gierthmuhlen

ISSN: 1759-4766

DOI:

Anno: 2014

Volume:

Fascicolo:

Editore:

Pag. iniziale:

Pag. finale:

Mechanism-based treatment in complex regional pain syndromes

Janne Gierthmühlen, Andreas Binder and Ralf Baron

Abstract | Complex regional pain syndromes (CRPS) are multifactorial disorders with complex aetiology and pathogenesis. Management of CRPS is challenging, partly because of a lack of clinical data regarding the efficacy of the various therapies, and partly because successful treatment of CRPS requires a multidisciplinary, patient-tailored approach. The pain in CRPS is often described as typical 'burning' neuropathic pain, and is accompanied by a variety of sensory, motor and autonomic signs and symptoms. Because research into therapies specifically in CRPS has been scarce, treatment for these syndromes has been largely based on therapeutic strategies adapted from neuropathic pain states; however, increased understanding of the pathogenesis of CRPS has provided the opportunity to develop mechanism-based treatments. The interactions between the multiple pathophysiological mechanisms that contribute to the development, progression and maintenance of CRPS remain poorly understood. This Review describes the challenges in linking the current theories and knowledge of pathophysiological mechanisms to the mode of actions of the different treatment approaches. We discuss the current treatment strategies for CRPS, including pharmacotherapy, sympathetic ganglion block interventions, psychological support, physiotherapy and occupational therapy, and establish the concept of mechanism-based treatment for CRPS.

Gierthmühlen, J. *et al. Nat. Rev. Neurol.* advance online publication 19 August 2014; doi:10.1038/nrneurol.2014.140

Introduction

Complex regional pain syndromes (CRPS), formerly known as Sudeck's dystrophy, algodystrophy, causalgia or reflex sympathetic dystrophy, are multifactorial pain disorders. 'Complex' refers to the varied clinical symptoms—such as sensory,[1] motor[2] and autonomic abnormalities[3,4]—that accompany the pain. 'Regional' addresses the regional distribution of signs and symptoms, which usually spread distally in the affected limb, extending beyond the innervation territory of any particular nerve or root. 'Pain' is the cardinal symptom of the disease.

Spontaneously occurring CRPS are rare; typically, CRPS develop after minor tissue injury or limb trauma.[5,6] CRPS are classified into two subtypes: CRPS type 1, with no definite evidence of a major nerve lesion, and CRPS type 2, in which nerve lesion can be demonstrated.[7] Thus, CRPS type 1, by definition, presents without any major nerve lesion and does formally not fulfil the criteria for neuropathic pain.[8] Sensory signs and symptoms of CRPS types 1 and 2 are almost identical, with the exception of stronger hypoaesthesia to mechanical stimuli in CRPS type 2, attributable to the nerve lesion.[6] CRPS type 1 and 2 might, therefore, represent one disease continuum with largely similar pathophysiology. In this Review, therefore, we will describe clinical presentation, mechanisms and their interactions largely without differentiation between CRPS types 1 and 2.

Clinical presentation of CRPS

The current diagnostic criteria[9] for CRPS are based on the main signs and symptoms: sensory, autonomic and motor abnormalities.[1–4] Less-specific symptoms of CRPS include the so-called neglect-like phenomena,[10–13] abnormal postures[14] and contractures,[15] mental health problems,[16] and sympathetically maintained pain (SMP).[17,18] The presence of these signs and symptoms varies between patients, and can change over time in a given individual patient. One very important clinical finding is the distal distribution of all signs and symptoms (Figure 1): the symptoms spread distally from the injured area in a glove-like or stocking-like manner,[1,5,19] leading to manifestation of signs and symptoms also in the hand and foot including all fingers (in CRPS on the upper extremity) or toes (CRPS of the lower extremity). Sensory disturbances can even extend to more-proximal areas of the

Division of Neurological Pain Research and Therapy, Department of Neurology, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Arnold-Heller-Strasse 3, Haus 41, 24105 Kiel, Germany (**J.G.**, **A.B.**, **R.B.**).

Correspondence to: J.G. j.gierthmuehlen@neurologie.uni-kiel.de

Competing interests
J.G. has received honoraria from Grünenthal and Pfizer. A.B. has received honoraria from Astellas, Allergan, Bayer, Boehringer Ingelheim, Grünenthal and Pfizer, and has participated in the advisory boards of Astellas, Boehringer Ingelheim, Genzyme, and Grünenthal. R.B. has received grant/research support from Pfizer, Genzyme and Grünenthal. He is a member of the IMI EuroPain collaboration, in which the following industry members are represented: Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Esteve, Grünenthal, Pfizer, UCB-Pharma and Sanofi Aventis. He has also received honoraria as a speaker from Astellas, Bayer-Schering, Boehringer Ingelheim, Desitin, Eisai, Eli Lilly, Genzyme, Grünenthal, Medtronic, Mundipharma, MSD, Pfizer, Sanofi Pasteur and Teva Pharma. He is a consultant for Abbvie, Allergan, Astellas, AstraZeneca, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Eli Lilly, Genzyme, Grünenthal, Medtronic, Merck, Mundipharma, Novartis, Pfizer and Sanofi Pasteur.

Key points

- Complex regional pain syndromes (CRPS) are multifactorial disorders; the heterogeneity of clinical signs and symptoms reflects different underlying pathophysiological mechanisms
- Peripheral mechanisms of CRPS include inflammation, peripheral sensitization and sympatho-afferent coupling
- Central mechanisms include neuroplastic changes, such as cortical reorganization, afferent–efferent feedback conflicts and central autonomic dysregulation
- Individual variation in pathophysiological mechanisms offer the opportunity for several mechanism-based treatment options
- To date, only a few clinical trials have assessed the long-term efficacy of therapies specifically for CRPS

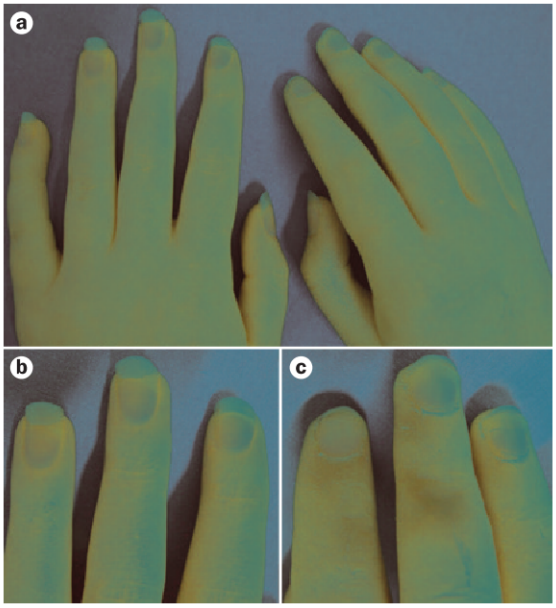

Figure 1 | Trophic disturbances in a patient with a complex regional pain syndrome of the hand. **a** | Comparison of unaffected (left) and affected (right) extremity shows distally distributed oedema, including the fingers, on the affected extremity. Comparing the **b** | unaffected extremity and the **c** | affected extremity reveals dry skin and reduced nail growth in the affected extremity.

same limb[20] and to previously unaffected limbs,[20–22] and motor deficits can occur in unaffected extremities.[23,24] Another important factor in the diagnosis of CRPS is the change in pain characteristics on developing the condition: many patients describe a sudden change from the initial, characteristically nociceptive pain after fracture or surgery to a typical neuropathic 'burning' pain.

The current diagnostic criteria for CRPS were established and validated relatively recently: the International Association for the Study of Pain defined the diagnostic criteria for CRPS in 1994.[25] Consequently, comparing the results from the studies that were conducted before uniform diagnostic criteria with the results obtained in the past 20 years is difficult. Different authors might not be describing CRPS but a syndrome with similar symptoms,[26] and findings regarding treatment of CRPS might be based on different populations, thereby limiting their usability.

Somatosensory abnormalities and pain

Pressure pain hyperalgesia is the most frequent somatosensory symptom in CRPS,[2] and can be observed in 66% of patients with CRPS type 1 and 73% of patients with CRPS type 2. In patients with CRPS of the upper extremity, spontaneous pain is present in 55% of patients with CRPS type 1, and in 76% of patients with CRPS type 2.[6] Pain on movement was found to be present in more than 60% of all patients,[6] and pain under orthostatic conditions (when the extremity hangs down), occurs in more than 50%.[1,19] The patients often describe the pain as tearing, burning or stinging; it is often reported to feel diffuse and be located deep within the extremity.[1,19] The deep somatic domain is likely to have a major role in CRPS (discussed below).

Some patients with CRPS display SMP, which manifests as spontaneous or evoked increases in pain in response to activation of the sympathetic nervous system.[27] However, it is important to acknowledge that SMP is not a cardinal symptom in all patients with CRPS, but should be regarded as a potential sign of CRPS.

Autonomic abnormalities and oedema

Vasomotor disturbances are common in CRPS: vasodilatation or vasoconstriction that result in differences of skin temperature and colour between the affected and the unaffected extremity are frequently observed.[5,6,9,28–30] 71–97% of patients report skin colour asymmetries[5,9,28,31] and 79–98% report temperature differences between the affected and unaffected extremity.[5,9,28,31] Sudomotor abnormalities (hyperhidrosis, and occasionally hypohidrosis, which is often observed in chronic CRPS) are reported in approximately half of patients.[3,5,9,28,31–33]

Presence of oedema, especially in acute CRPS, is described in 55–89% of cases.[5,6,9,19,28,34] Similar to other autonomic abnormalities, oedema can be triggered by external stimuli, such as pain or orthostatic conditions as well as alterations in vascular tone.[3,19,33,35,36] Over the course of the disease, oedema usually becomes less frequent and/or severe, and the tendency to develop oedema can eventually disappear completely,[37] although a disposition for swelling was reported by 90% of patients even after 15 years' duration of CRPS.[31]

Motor and trophic abnormalities

75–88% of patients with CRPS report experiencing motor abnormalities,[9,28] which is in line with the motor abnormalities found upon clinical examination.[2,6,9,19,33] Among motor abnormalities, 80% of patients describe a decreased range of motion and 75% report weakness in the affected limb.[28] The patients experience difficulties particularly with complex movements such as closing the fist and opposition of the first and fifth digits,[22,36] which can to some extent be explained by reduced movements of associated joints due to oedema and muscle hypertension in acute CRPS; in chronic CRPS, contraction and fibrosis of palmar or plantar aponeurosis can limit motoric movement of the hand.[33] Impaired central processing of proprioceptive information might also be involved.[38] Although less frequent, movement disorders—such as

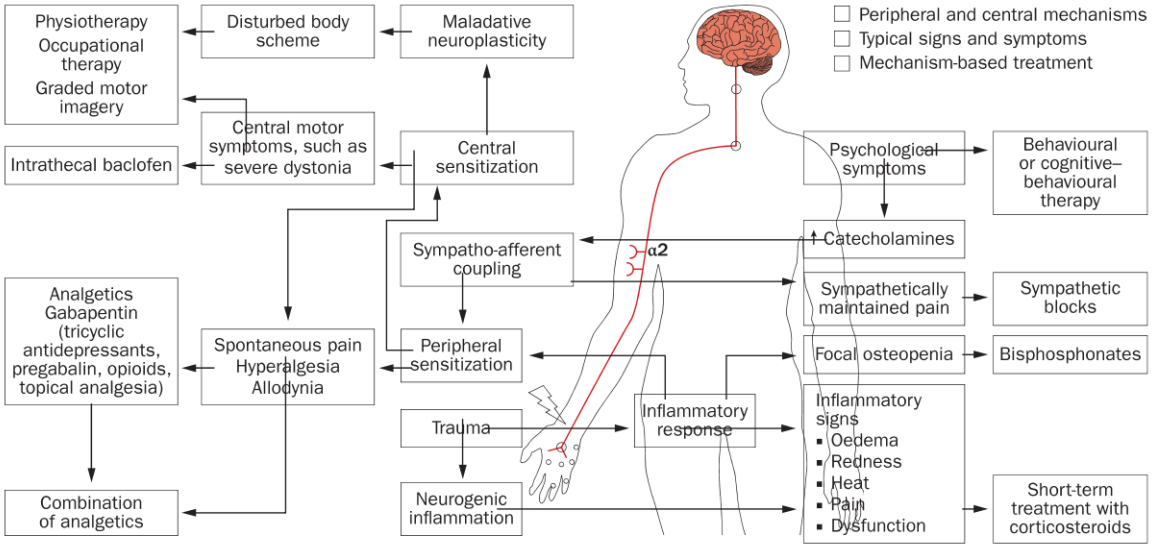

Figure 2 | Pathophysiology and mechanism-based treatment options in CRPS. Hypothesized interaction between peripheral and central mechanisms in CRPS, based on Bruehl *et al.*:[166] peripheral and central mechanisms (yellow boxes) lead to a multitude of different typical signs and symptoms (pink), which can guide selection of mechanism-based treatment options (blue). The onset of CRPS is usually preceded by a trauma—such as a radius fracture—that results in an inflammatory response and neurogenic inflammation, which can induce focal osteopenia. Release of cytokines from the inflamed region leads to peripheral sensitization, which brings forth central sensitization and maladaptive neuroplasticity, resulting in central motor symptoms and disturbances of the body scheme. Sympatho-afferent coupling produces sympathetically maintained pain. Psychogenic stress can result in increased release of catecholamines, which can generate and further exacerbate pain. CRPS are complex diseases, and successful therapy requires multifactorial treatment consisting of pharmacotherapy, interventional therapy (such as sympathetic blocks or intrathecal baclofen administration), physiotherapy (including graded motor imagery), occupational therapy and psychological treatment. Abbreviation: CRPS, complex regional pain syndromes.

bradykinesia, dystonia, myoclonus and tremor—have also been reported in patients with CRPS.[2,5,19,39–42]

Trophic changes, such increased or decreased hair or nail growth, tissue dystrophy, and thin or shiny atrophy of the skin, subcutaneous tissue, muscles and bone (patchy osteoporosis, focal osteopenia) are also characteristic findings in CRPS (Figure 1).[43]

Towards mechanism-based treatment

Both types of CRPS present with typical signs that are characteristic of neuropathic pain (spontaneous, burning pain, allodynia and pain occurring in the area with sensory abnormalities;[8] Figure 2). Several pathological mechanisms known from other neuropathic pain states have been tentatively 'transferred' to CRPS as an attempt to explain the pathophysiology and to address the hypothesis that different clinical signs reflect different underlying mechanisms.[44]

CRPS are multifactorial disorders that cannot be explained by a single underlying mechanism, such as peripheral inflammation or dysfunction of the sympathetic nervous system.[45] The multitude and complexity of pathophysiological mechanisms involved in CRPS are thought to be responsible for the heterogeneity of the clinical presentation, and also explain the difficulty of establishing evidence-based treatment regimens for CRPS.

Evidence for therapeutic strategies specific to CRPS, and therapies targeting distinct mechanisms rather than just alleviating symptoms of CRPS, is scarce.[46] Attempts at mechanism-based treatment in CRPS rely mainly on translating findings from other pain syndromes, predominantly neuropathic pain states.[47,48] Application of pharmacotherapies that are efficient in neuropathic pain to CRPS is not without problems, however. Most randomized controlled trials (RCTs) investigating neuropathic pain have been conducted in patients with postherpetic neuralgia or diabetic peripheral neuropathy, differ substantially in research design and outcomes as well as number of included patients, and often have a short treatment duration, despite the fact that most neuropathic pain conditions are chronic.[49] Keeping these difficulties in mind, we review here the pathophysiological mechanisms and possible treatment options in CRPS. It is important to note that the choice of medication in the individual patient depends on comorbidities, drug interactions and tolerance of adverse effects, as well as risk of misuse and abuse.[49]

Peripheral mechanisms

Nerve injury leads to spontaneous ectopic discharges and hyperexcitability of primary afferent nociceptors[50] by triggering changes in the expression of neurotransmitters, neuromodulators, growth factors, receptors and neuroactive molecules in primary afferent neurons.[51] This process results in peripheral sensitization, which subsequently enhances nociception and results in hypersensitivity to pain.[52] Micrography recordings have demonstrated spontaneous pathological nerve impulse activity in nociceptive neurons in some patients with CRPS,[53] supporting the idea that peripheral sensitization is involved in CRPS.

Targeting peripheral sensitization

Although modulation of peripheral nerve activity is a standard approach in pain treatment, studies investigating the efficacy of suppression of peripheral nerve activity in CRPS are scarce. The efficacy of NSAIDs, carbamazepine or other systemically acting sodium channel-modulating anticonvulsants has not been assessed in placebo-controlled trials. In a small trial, intravenously administered lidocaine in CRPS was shown to reduce the thermal and mechanical allodynic area.[54] Overall, however, evidence for the use of lidocaine in the treatment of CRPS received a low rating due to a lack of studies with a large sample size and the unknown long-term effects of lidocaine on pain and other symptoms in CRPS.[55]

Sympathetically maintained pain

Inflammatory processes and sympathetic–afferent coupling contribute to peripheral sensitization in CRPS (Figure 2), meaning that corticosteroids or sympatholytic therapies could result in peripheral desensitization. In some patients, intradermal noradrenaline injection can aggravate CRPS,[56,57] suggesting involvement of noradrenergic sensitization of peripheral afferent nociceptive fibres and a pathological interaction between the efferent sympathetic and the afferent system. This efferent–afferent coupling can take place directly through activation of noradrenaline-releasing sympathetic efferent fibres and α-adrenoreceptor-expressing nociceptive afferents, or indirectly either through vasoconstriction that influences the micromilieu of nociceptors or through macrophage activation, which results in release of inflammatory mediators.[27] Both direct and indirect mechanisms result in activation and further sensitization of nociceptive fibres.

Sympathetic ganglion blocks

Noradrenergic sensitization of afferent fibres can be treated by blocking noradrenaline release from sympathetic fibres locally within the area of pain (regional sympatholysis) or proximally at the sympathetic ganglion. Despite encouraging clinical experience and many positive results in uncontrolled studies in patients with CRPS, it should be noted that many of these studies lack specificity, long-term follow-ups and evaluation of the different interventional procedures. The efficacy of sympatholytic procedures in CRPS has, therefore, been debated.[58] For example, one controlled trial of a sympathetic ganglion block approach demonstrated that local anaesthetic and saline had the same immediate effects on pain, but on re-evaluation after 24 h, local anaesthetics were more efficacious than placebo,[59] suggesting that evaluation of sympatholytic interventions should be done after 24 h. By contrast, repetitive stellate ganglion blocks as an add-on therapy did not significantly reduce pain 1 month after the injections.[60] In light of these conflicting results, uncontrolled studies must be interpreted with caution, particularly because only a minority of them assess the long-term effects of sympatholysis.[61]

Noradrenaline release inhibitors

A meta-analysis assessing the efficacy of intravenous regional sympatholysis (IVRS) by the noradrenaline release inhibitor guanethidine did not show superior pain relief over placebo,[55] but transdermal application of clonidine, which blocks noradrenaline release by activating α2 receptors on the peripheral sympathetic terminals, reduced hyperalgesia in patients with SMP.[62] However, the results from this open-label study with four patients must be interpreted with caution.

Growing evidence suggests that only a subgroup of patients will develop a sympathetically maintained pain component, and that this component might vary between individuals, meaning that the design of trials using sympatholytic procedures need to be re-evaluated. Furthermore, controlled studies assessing the acute as well as the long-term effects of sympathetic blockade and IVRS on pain and other CRPS symptoms are desperately needed.

Inflammatory response

As mentioned above, CRPS can develop after tissue injury, and might, in some cases, be triggered by an injury affecting a peripheral nerve. As a response to tissue damage, various inflammatory cells, such as lymphocytes, monocytes, mast cells and neutrophils, migrate to the location of injury and release inflammatory mediators such as prostaglandin E2, bradykinin, ATP, protons, nerve growth factors, and proinflammatory cytokines such as tumour necrosis factor (TNF) and IL-1β, which induce pain hypersensitivity.[63–65] After nerve damage, these mediators can also be released from primary sensory terminals or damaged axons and their enclosing Schwann cells.[66] Increased levels of proinflammatory cytokines and decreased levels of anti-inflammatory cytokines have been observed in blister fluids,[67,68] skin,[69] blood,[70] and cerebrospinal fluid[71] of patients with CRPS.[72]

Overall, the inflammatory response increases blood flow and vascular permeability,[63] leading to all five cardinal signs of inflammation described by Celsus and Galen almost 2,000 years ago: *dolor* (pain), *calor* (heat), *rubor* (redness), *tumor* (swelling), and *functio laesa* (loss of function). These signs are often present in acute CRPS.

Neurogenic inflammation

The aforementioned nonspecific inflammatory response is amplified by neurogenic inflammation: besides the orthodromic conduction of nerve impulses towards the dorsal root ganglion, activation and sensitization of nociceptors also leads to antidromic excitation, which results in release of vasoactive peptides, such as calcitonin gene-related peptide (CGRP) and substance P, from the peripheral nerve terminals.[73,74] These peptides induce vasodilatation and plasma extravasation around the peripheral nerve endings, thereby contributing to local oedema, heat and redness. Increased neurogenic plasma extravasation indicating neuropeptide release has been observed in CRPS,[35,75] and patients with CRPS can have increased serum levels of CGRP[76] and substance P.[77]

Corticosteroids and immunomodulatory drugs

Inflammatory processes in CRPS have been targeted with corticosteroids and free radical scavengers; however, the trials assessing the efficacy of steroids have produced conflicting results. Orally administered prednisone efficiently improved clinical symptoms in acute CRPS,[78] whereas a single intrathecal methylprednisolone bolus was not effective at improving chronic CRPS.[79] Three intravenous regional blocks with 40 mg methylprednisolone and 2% lidocaine were no more effective than placebo.[80] In summary, oral steroids might be an effective treatment for patients with CRPS in whom inflammatory processes—oedema, increased local temperature and reddening of skin—are clinically detectable; however, evidence for pain reduction is weak,[81,55] and no recommendations regarding dosage or treatment duration can be given at this stage. Long-term use of steroids should be avoided because of adverse effects.

A trial using the anti-TNF monoclonal antibody infliximab was discontinued because infliximab was not found to be superior to placebo in alleviating pain.[82] No trials have been conducted to assess the efficacy of other immunomodulatory therapies, such as immunosuppressive drugs.

Free radical scavengers

One study comparing the efficacy of the free radical scavengers dimethylsulphoxide (DMSO; topical administration) and *N*-acetylcysteine (NAC, oral administration) demonstrated that both drugs were effective in CRPS. DMSO seems to be more effective in 'warm' CRPS (characterized by increased skin temperature in the affected extremity, along with oedema, redness and other signs of inflammation) and NAC in 'cold' CRPS (characterized by reduced temperature and tissue atrophy); the efficacy of both drugs tends to decrease over disease duration.[83] Other studies investigating DMSO in CRPS have obtained conflicting results, so the overall level of evidence for reduction of pain in CRPS was judged to be low.[55]

Autoimmunity in CRPS

Some cases of CRPS might be associated with an autoantibody-mediated autoimmune aetiology.[84] Several observations support this hypothesis: intravenous immunoglobulin treatment can reduce pain in CRPS,[85] and serum from patients with CRPS is much more likely to contain IgM and IgG antibodies against different bacterial and viral surface epitopes than is serum from healthy controls, suggesting that aberrant autoimmune activity might produce cross-reactive autoantibodies.[84] In addition, serum from patients with CRPS can contain autoantibodies against autonomic nervous system structures.[86,87] Pre-existing circulating autoantibodies have been hypothesized to become pathogenic after the onset of CRPS; these antibodies have been suggested to sustain sensitization, thereby maintaining chronic CRPS.[84] It should be noted, however, that the relevance of these findings remains unclear and, given the high costs of intravenous immunoglobulin treatment, further research is necessary to confirm this hypothesis.

The role of deep somatic tissue in CRPS

Processes involved in CRPS are not restricted to the skin; deep somatic tissue (muscles and/or bones) seems also to have an important role in the pathophysiology of CRPS. Infusion of low-pH fluid into the muscle causes pain that is characterized as very similar to CRPS-related pain.[88] Furthermore, development of CRPS often follows a deep-tissue injury such as a fracture or sprain, and pressure pain hyperalgesia,[2] bone atrophy[89] and an increased periarticular uptake in the delayed phase of three-phase bone scintigraphy[90,91] are frequently observed in CRPS. The suggested involvement of deep somatic tissue is supported also by the observation that in CRPS with SMP, sympathetic blocks (complete blockade of sympathetic outflow) result in more-pronounced relief of spontaneous pain than does selective sympathetic cutaneous modulation.[18] Altogether, these findings suggest that the CRPS pain is, at least in part, generated in deep somatic structures. Despite the importance of deep somatic tissue involvement in CRPS, its role has been largely neglected in clinical research.

Bisphosphonates regulate bone metabolism, but they also have an analgesic effect, possibly by modulating bone resorption. Early treatment with oral or intravenous bisphosphonates has been shown to reduce pain and improve function in CRPS;[92–94] however, a recently published systematic review concludes that the evidence for the use of bisphosphonates for the treatment of pain in CRPS is of low quality, and that the reported effects might be specific to CRPS accompanied by clinical osteopenia or osteoporosis.[55] Further evaluation, therefore, seems to be warranted. Regarding calcitonin, however, the evidence seems clearer that its application is not useful.[95,96]

Central mechanisms

Peripheral sensitization of afferent C fibres can trigger central sensitization—a prolonged but reversible increase in the excitability and synaptic efficacy of neurons in the spinal cord, brainstem and brain.[97,98] Central sensitization is thought to contribute to the chronification of pain in CRPS.[43,97] One important underlying mechanism of central sensitization and subsequent generation of pain hypersensitivity is the release of excitatory neurotransmitters into the spinal cord, where calcium channels and opioid receptors control both neuronal activity and transmitter release,[99] leading to activation of neurokinin and *N*-methyl-D-aspartate (NMDA) receptors and pain processing.[98,100] Clinical manifestations of central sensitization—dynamic tactile allodynia, secondary punctate hyperalgesia, and/or enhanced temporal summation[44]—are often present in CRPS.[5,6,19,101,102]

Endogenous pain modulation

Endogenous pain modulation enables regulation of pain-related signals in the spinal cord. The brainstem has an essential role in endogenous pain modulation because both descending inhibitory and excitatory systems originate from the brainstem.[103,104] Patients with CRPS express both decreased adaptation to painful

stimuli and increased areas of hyperalgesia on affected hands, suggesting a shift from inhibition to facilitation of nociceptive input, possibly due to differential activation of subcomponents of the endogenous pain modulatory system.[105]

Drugs targeting central sensitization

To date, the use of tramadol and strong oral opioids in CRPS has not been studied in RCTs. Although opiates have proven efficacy in several high-quality RCTs in patients with different types of neuropathic pain, adverse effects such as constipation, nausea and sedation, as well as concerns regarding long-term safety—including risk of hypogonadism, immunological changes, misuse or abuse, and opioid-induced hyperalgesia—limit their use.[49] Therefore, the International Association for the Study of Pain generally recommends opioids only as a second-line treatment.[49] This recommendation applies to use of opioids in CRPS; recently published guidelines for treatment of CRPS suggest that strong opioids should not be used in this patient group[46] due to insufficient evidence for their efficacy.[81] Nevertheless, under certain circumstances, such as acute neuropathic pain or episodic exacerbations of severe neuropathic pain, opioids can be used as first-line treatments.[49] It is important to note, however, that no prospective, controlled long-term (>3 months) studies of oral opioid use in chronic neuropathic pain have been conducted. Strong opioids should be used in moderate dosages and discontinued if a patient-initiated dose increase is documented or adverse effects occur.

Gabapentin and pregabalin reduce the release of excitatory amino acids and neuropeptides by modulation of calcium channels in the spinal cord neurons. A randomized, double-blind, placebo-controlled crossover study found that gapapentin improved sensory deficits but showed no clear benefit in terms of pain reduction.[106] Overall, although evidence for the use of gabapentin in CRPS is scarce[55] and no trials assessing the efficacy of pregabalin exist, the use of calcium-channel modulating agents in CRPS should be considered because of the neuropathic nature of pain in CRPS;[46] adverse effects, however, remain an important consideration.[55,46]

Ketamine, dextromethorphan and memantine have NMDA receptor-blocking properties and are already in clinical use, making them attractive candidates for treating CRPS. Intravenously administered ketamine demonstrated analgesic efficacy in CRPS in two RCTs,[107,108] however, both studies had a small sample size and beneficial effects were not sustained beyond 4 weeks[107] or 11 weeks[108] after treatment discontinuation. Topical administration of ketamine on the affected extremity has been demonstrated to inhibit allodynia to light brushing and hyperalgesia to punctate stimulation[109]—a limitation to this study was that overall pain intensity was not assessed as a clinical outcome. A ketamine–morphine combination treatment has been shown to be more effective than placebo in reducing pain and normalizing cerebral pain processing, as observed by functional MRI.[110] Nevertheless, the overall quality of evidence regarding treatment of CRPS-related pain with intravenous or topical ketamine, memantine or dextromethorphan is limited,[55,111] and adverse effects limit their application. Further studies are necessary to assess the efficacy and risk–benefit ratios of these approaches.

Epidural spinal cord stimulation (SCS) has also been suggested to reduce central sensitization. One study investigating SCS combined with physiotherapy in patients with treatment-refractory CRPS showed that in the first 2 years following implantation, pain reduction was more pronounced in the patients in the SCS group than in patients receiving physiotherapy alone;[112,113] however, 5 years following implantation, the difference between the two groups was undetectable,[114] and the rate of complications in the SCS group (caused for example, by malfunctioning of the pulse generator or lead dislocation) increased. When the complication rate and costs are taken into account, SCS seems to be useful only in selected patients, after a strict diagnostic evaluation.

Addressing descending inhibitory pathways

Antidepressants (tricyclic antidepressants and selective serotonin and noradrenaline reuptake inhibitors) are thought to strengthen descending inhibitory activity, and have proven to be effective in different neuropathic pain conditions, but there is no direct evidence from RCTs to support the use of antidepressants in CRPS.[55,81]

Clonidine, an α2 adrenergic agonist, modulates the descending inhibitory pathways. In selected patients with severe refractory CRPS, epidural application of clonidine reduced pain up to 6 h after treatment, but it had important adverse effects, such as sedation and hypotension.[115] Due to limitations in study design, low sample size, and short follow-up duration of only 6 h, the level of evidence for the efficacy of epidural clonidine in treatment of CRPS was judged to be low[55] and, given the potential adverse effects and invasive procedure, its administration should be limited to cases that are refractory to other treatments. Oral antidepressants, however, should be considered to address the neuropathic component of pain in CRPS.[46]

Afferent–efferent feedback disturbance

Body perception disturbances

Processing of nociceptive stimuli is not restricted to the nociceptive afferent pathways, but involves an extensive cortical network that includes the somatosensory, insular and cingulate areas, as well as frontal and parietal areas that are necessary for conscious perception, attentional modulation and control of vegetative reactions.[116–118] Dysfunction of proprioceptive afferent feedback from the affected tissue to subcortical and cortical centres involved in perception of the body and regulation of somatomotor and visceromotor reactions has been hypothesized to have a major role in the mechanisms that underlie CRPS.[45,119] Some patients with CRPS show symptoms that are reminiscent of neurological neglect,[10,11,13,120–122] although in contrast to the classic neurological neglect, patients are aware of their disturbances. This finding has led to the suggestion that these

neglect-like symptoms,[12] which are limb-specific and correlate positively with intensity of pain and decreased tactile acuity,[123,124] might be better described as 'body perception disturbance'.[12]

Some patients with CRPS exhibit shrinkage of the somatotopic map within the primary somatosensory cortex that represents the affected extremity. Pain intensity and mechanical allodynia correlate with the shrinkage of the somatotopic map,[125] and clinical improvement correlates with restoration of the map.[126,127] Changes in cortical representation due to deafferentiation or enhanced nociceptive input are likely to contribute to the observed body perception disturbances, and these changes might, in turn, lead to disruption of afferent–efferent feedback.

The importance of visual control

Nociceptive processing is known to be influenced by visual input.[128–132] When participants look at their own body, their neural responses to painful stimuli are reduced and they report that the perceived intensity of pain is decreased—a phenomenon called visually induced analgesia. Visual distortion of the body size can modulate pain perception. For example, visually shrinking the appearance of a phantom limb reduced phantom limb pain,[133] and in chronic hand pain, similar visual shrinkage of the limb decreased movement-evoked pain and swelling.[134] A mismatch between the perceived location of the stimulus within an anatomical (or somatotopic) and visuo–spatial frame of reference has been suggested to account for this phenomenon.[128]

Compared with healthy controls, patients with CRPS display difficulties in positioning of both the affected and unaffected limb, and position accuracy of the affected limb significantly improves with visual control.[135] Vision, body perception disturbance and pain perception are known to be closely linked in CRPS.[136] Conflicting visual information can generate pain and/or sensory disturbances, asymmetric peripheral vasomotor sympathetic responses and dystonic reactions in some patients with CRPS.[137,138]

Conflict of sensory and motor information

In the presence of altered body perception and cortical reorganization, the motor and sensory maps no longer accurately portray the actual location of body parts, potentially resulting in disrupted sensorimotor function, which can lead to pain generation.[136,139,140] Indeed, a study of healthy volunteers demonstrated that sensorimotor conflict, induced by incongruent movements of corresponding limbs while viewing one of the limbs in a mirror, could induce pain and sensory disturbances, such as differences in temperature perception in the hidden limb.[141] In CRPS, touching the unaffected extremity while viewing it in a mirror induced pain or paraesthesia at the corresponding site on the affected hidden limb.[142]

Re-establishing the afferent–efferent mismatch

Physiotherapy and occupational therapy are considered to be the most important treatments in CRPS.[143] Clinical experience and RCTs clearly indicate that physiotherapy is of the utmost importance to reduce pain and restore the function of the affected limb. Occupational therapy can further facilitate rehabilitation.[144–146] Standardized physiotherapy has been shown to provide long-term pain relief and functional improvement in children with CRPS.[147]

The incongruence between motor intention, proprioception and vision has been hypothesized to result in an affective sensation of pain; therapy might, therefore, be best directed at restoring the integrity of cortical information processing.[148] Indeed, pain and other pathological features of CRPS were alleviated when, once a day for 2 weeks, patients performed a target-pointing task while wearing prismatic goggles that produced a visual displacement toward the unaffected side.[149,150] Furthermore, mirrored visual feedback is a common treatment in CRPS, although evidence of efficacy is mainly based on studies assessing its benefits in post-stroke CRPS.[55] Graded motor imagery, consisting of a fixed-sequence combination of a hand laterality recognition task, imagined hand movements and mirror therapy has been shown to reduce pain and improve function in CRPS,[151,152] but the evidence should be interpreted with caution because of the small sample size and the methodological limitations of these studies.[55]

Central motor disorders

Intrathecally administered baclofen—a γ-aminobutyric acid receptor type B agonist—has been shown to be effective in the treatment of dystonia in CRPS;[153,154] however, the studies reported many complications and adverse effects associated with baclofen and the intrathecal delivery device, including somnolence, psychiatric symptoms, urine retention, post-puncture headache, leakage of cerebrospinal fluid, and infection and dislodgement or migration of the catheter device.[154] The small sample sizes and limitations of study design mean that these studies provide only level 3 evidence in support of intrathecal baclofen in CRPS.[111]

Psychological symptoms

Various psychological symptoms such as anxiety, depression and personality disorders are not uncommon in CRPS,[155,156] but whether these symptoms predispose patients to the development of CRPS, or are secondary to CRPS (for example, resulting from chronic pain), is under debate. According to most studies, the psychological characteristics of patients with CRPS do not differ from those of patients with other chronic pain conditions.[157–161] Furthermore, most prospective studies have not found unique psychological characteristics or increased frequency of psychological symptoms in patients who developed CRPS compared with those who recovered from the initial injury uneventfully.[162–164] Indeed, a recent review concludes that there is no support for specific personality or psychopathology predictors of CRPS.[16]

Despite these findings, CRPS is clearly associated with negative psychological health outcomes, such as

increased depression and anxiety as a consequence of pain and disability,[16] and psychological and behavioural factors can, in turn, contribute to the pathophysiology of CRPS. One possible mechanism by which psychological symptoms can influence CRPS is systemic catecholamine release due to chronic stress as a result of depression, anxiety, pain or other life stressors, which can result in increased perception of pain and exacerbation of vasomotor signs via upregulation of adrenergic receptors and sympatho-afferent coupling.[165–167]

Supporting the idea that psychological comorbidities can exacerbate CRPS, a prospective, randomized, single-blind trial of physical therapy and cognitive–behavioural treatment for children and adolescents with CRPS showed a long-lasting improvement of pain and motor function.[168] To date, this is the only RCT to investigate the efficacy of psychological interventions in CRPS; however, several uncontrolled studies suggest that various forms of relaxation training, biofeedback, and cognitive and behaviourally focused interventions could be beneficial.[111]

Conclusions

The pathophysiology of CRPS is complex. Various approaches to understand and explain the pathophysiology of CRPS have resulted in several treatment opportunities, but only a few studies have evaluated mechanisms-based treatment options. One important explanation for the lack of such trials might be the relatively low prevalence of CRPS and the interindividual variations in clinical signs and symptoms, which reflect the heterogeneity of the underlying mechanisms. Network-based multicentre studies could provide large samples of patients, improve opportunities for stratification, and thereby aid evaluation of potential treatments. CRPS is a severe disease, and successful treatment would ideally require a multidisciplinary approach consisting of pharmacotherapy, interventional treatment, physiotherapy, occupational therapy and psychological counselling or treatment. Such an approach, however, makes the investigation of single mechanism-based treatment options difficult. Research into mechanism-based treatment in CRPS will be a tightrope walk between what is ethically possible and what is necessary to improve treatment of CRPS and, hence, the quality of life of patients.

Review criteria

For this Review, a search for (preferably) recently published original articles focusing on pathophysiology and treatment of complex regional pain syndromes (CRPS) was performed in MEDLINE and PubMed. The main search terms used were "complex regional pain syndrome", "CRPS", "reflex sympathetic dystrophy", "Sudeck", "algodystrophy", "pathophysiology", "mechanisms", "treatment", "randomized controlled trial" and the specific pathophysiological mechanism addressed, such as "sympathetically-maintained pain", "inflammation" or "central sensitization", alone and in combination with the main search terms. All articles identified full-text papers written in English or German. We also searched the reference lists of identified articles for further relevant papers. When not specifically mentioned, only studies conducted in adult patients with either CRPS type 1 or 2 were included.

1. Oaklander, A. L. & Birklein, F. in *CRPS: Current Diagnosis and Therapy* Vol. 32 Ch. 5 (eds Wilson, P. R. *et al.*) 59–79 (IASP Press, 2005).
2. Van Hilten, J. J., Blumberg, H. & Schwartzman, R. J. in *CRPS: Current Diagnosis and Therapy* Vol. 32 Ch. 8 (eds Wilson, P. R. *et al.*) 119–137 (IASP Press, 2005).
3. Sandroni, P. & Wilson, P. R. in *CRPS: Current Diagnosis and Therapy* Vol. 32 Ch. 7 (eds Wilson, P. R. *et al.*) 107–118 (IASP Press, 2005).
4. Wasner, G. & Baron, R. *in CRPS: Current Diagnosis and Therapy* Vol. 32 Ch. 6 (eds Wilson, P. R. *et al.*) 81–106 (IASP Press, 2005).
5. Veldman, P. H., Reynen, H. M., Arntz, I. E. & Goris, R. J. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet* **342**, 1012–1016 (1993).
6. Gierthmuhlen, J. *et al.* Sensory signs in complex regional pain syndrome and peripheral nerve injury. *Pain* **153**, 765–774 (2012).
7. Harden, N. & Bruehl, S. in *CRPS: Current Diagnosis and Therapy* Vol. 32 Ch. 4 (eds Wilson, P. R. *et al.*) 45–58 (IASP Press, 2005).
8. Treede, R. D. *et al.* Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* **70**, 1630–1635 (2008).
9. Harden, R. N. *et al.* Validation of proposed diagnostic criteria (the "Budapest Criteria") for complex regional pain syndrome. *Pain* **150**, 268–274 (2010).
10. Galer, B. S. & Jensen, M. Neglect-like symptoms in complex regional pain syndrome: results of a self-administered survey. *J. Pain Symptom Manage.* **18**, 213–217 (1999).
11. Frettloh, J., Huppe, M. & Maier, C. Severity and specificity of neglect-like symptoms in patients with complex regional pain syndrome (CRPS) compared to chronic limb pain of other origins. *Pain* **124**, 184–189 (2006).
12. Lewis, J. S., Kersten, P., McCabe, C. S., McPherson, K. M. & Blake, D. R. Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). *Pain* **133**, 111–119 (2007).
13. Moseley, G. L., Gallace, A. & Spence, C. Space-based, but not arm-based, shift in tactile processing in complex regional pain syndrome and its relationship to cooling of the affected limb. *Brain* **132**, 3142–3151 (2009).
14. Bank, P. J., Peper, C. L., Marinus, J., Beek, P. J. & van Hilten, J. J. Deficient muscle activation in patients with complex regional pain syndrome and abnormal hand postures: an electromyographic evaluation. *Clin. Neurophysiol.* **124**, 2025–2035 (2013).
15. Mendicino, R. W., Kim, C., Kabazie, A. J. & Catanzariti, A. R. Correction of severe foot and ankle contracture due to CRPS using external fixation and pain management: report of a pediatric case. *J. Foot Ankle Surg.* **47**, 434–440 (2008).
16. Lohnberg, J. A. & Altmaier, E. M. A review of psychosocial factors in complex regional pain syndrome. *J. Clin. Psychol. Med. Settings* **20**, 247–254 (2013).
17. Baron, R., Schattschneider, J., Binder, A., Siebrecht, D. & Wasner, G. Relation between sympathetic vasoconstrictor activity and pain and hyperalgesia in complex regional pain syndromes: a case–control study. *Lancet* **359**, 1655–1660 (2002).
18. Schattschneider, J., Binder, A., Siebrecht, D., Wasner, G. & Baron, R. Complex regional pain syndromes: the influence of cutaneous and deep somatic sympathetic innervation on pain. *Clin. J. Pain* **22**, 240–244 (2006).
19. Birklein, F., Riedl, B., Sieweke, N., Weber, M. & Neundorfer, B. Neurological findings in complex regional pain syndromes—analysis of 145 cases. *Acta Neurol. Scand.* **101**, 262–269 (2000).
20. Rommel, O. *et al.* Hemisensory impairment in patients with complex regional pain syndrome. *Pain* **80**, 95–101 (1999).
21. van Rooijen, D. E., Marinus, J. & van Hilten, J. J. Muscle hyperalgesia is widespread in patients with complex regional pain syndrome. *Pain* **154**, 2745–2749 (2013).
22. Huge, V. *et al.* Complex interaction of sensory and motor signs and symptoms in chronic CRPS. *PLoS ONE* **6**, e18775 (2011).
23. Ribbers, G. M., Mulder, T., Geurts, A. C. & den Otter, R. A. Reflex sympathetic dystrophy of the left hand and motor impairments of the unaffected right hand: impaired central motor processing? *Arch. Phys. Med. Rehabil.* **83**, 81–85 (2002).
24. Schilder, J. C. *et al.* Motor control in complex regional pain syndrome: a kinematic analysis. *Pain* **153**, 805–812 (2012).
25. Reinders, M. F., Geertzen, J. H. & Dijkstra, P. U. Complex regional pain syndrome type I: use of the International Association for the Study of Pain diagnostic criteria defined in 1994. *Clin. J. Pain* **18**, 207–215 (2002).

26. Wilson, P. & Bogduk, N. in *CRPS: Current Diagnosis and Therapy* Vol. 32 Ch. 3 (eds Wilson, P. R. *et al.*) 19–41 (IASP Press, 2005).
27. Jänig, W. in *Pain* 1st edn Vol. 5 Ch. 5.17 (eds Basbaum, A. I. *et al.*) 194–225 (Academic Press, 2008).
28. Harden, R. N. & Bruehl, S. P. Diagnosis of complex regional pain syndrome: signs, symptoms, and new empirically derived diagnostic criteria. *Clin. J. Pain* **22**, 415–419 (2006).
29. Wasner, G., Schattschneider, J., Heckmann, K., Maier, C. & Baron, R. Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value. *Brain* **124**, 587–599 (2001).
30. Krumova, E. K. *et al.* Long-term skin temperature measurements—a practical diagnostic tool in complex regional pain syndrome. *Pain* **140**, 8–22 (2008).
31. Schwartzman, R. J., Erwin, K. L. & Alexander, G. M. The natural history of complex regional pain syndrome. *Clin. J. Pain* **25**, 273–280 (2009).
32. Sandroni, P. *et al.* Complex regional pain syndrome I (CRPS I): prospective study and laboratory evaluation. *Clin. J. Pain* **14**, 282–289 (1998).
33. Birklein, F. in *The Handbook of Clinical Neurology: Pain* 1st edn Vol. 81 Ch. 3 (eds Cervero, F. & Jensen, T. S.) 529–546 (Elsevier B.V., 2006).
34. Schurmann, M., Gradl, G., Andress, H. J., Furst, H. & Schildberg, F. W. Assessment of peripheral sympathetic nervous function for diagnosing early post-traumatic complex regional pain syndrome type I. *Pain* **80**, 149–159 (1999).
35. Weber, M., Birklein, F., Neundorfer, B. & Schmelz, M. Facilitated neurogenic inflammation in complex regional pain syndrome. *Pain* **91**, 251–257 (2001).
36. Rommel, O. & Maihofner, C. in *CRPS—Complex Regional Pain Syndrome* 1st edn Ch. D (eds Jänig, W. *et al.*) 63–81 (SUVA, 2013).
37. Birklein, F., Riedl, B., Griessinger, N. & Neundorfer, B. Komplexes regionales Schmerzsyndrom Klinik und autonome Störung während akuter und chronischer Krankheitsstadien. [German]. *Nervenarzt* **70**, 335–341 (1999).
38. Bank, P. J., Peper, C. L., Marinus, J., Beek, P. J. & van Hilten, J. J. Motor dysfunction of complex regional pain syndrome is related to impaired central processing of proprioceptive information. *J. Pain* **14**, 1460–1474 (2013).
39. Schwartzman, R. J. & Kerrigan, J. The movement disorder of reflex sympathetic dystrophy. *Neurology* **40**, 57–61 (1990).
40. Deuschl, G., Blumberg, H. & Lücking, C. H. Tremor in reflex sympathetic dystrophy. *Arch. Neurol.* **48**, 1247–1252 (1991).
41. van der Laan, L., Veldman, P. H. & Goris, R. J. Severe complications of reflex sympathetic dystrophy: infection, ulcers, chronic edema, dystonia, and myoclonus. *Arch. Phys. Med. Rehabil.* **79**, 424–429 (1998).
42. van Hilten, J. J., van de Beek, W. J., Vein, A. A., van Dijk, J. G. & Middelkoop, H. A. Clinical aspects of multifocal or generalized tonic dystonia in reflex sympathetic dystrophy. *Neurology* **56**, 1762–1765 (2001).
43. Borchers, A. T. & Gershwin, M. E. Complex regional pain syndrome: a comprehensive and critical review. *Autoimmun. Rev.* **13**, 242–265 (2014).
44. Baron, R. Mechanisms of disease: neuropathic pain—a clinical perspective. *Nat. Clin. Pract. Neurol.* **2**, 95–106 (2006).
45. Janig, W. & Baron, R. Complex regional pain syndrome: mystery explained? *Lancet Neurol.* **2**, 687–697 (2003).
46. Cossins, L. *et al.* Treatment of complex regional pain syndrome in adults: a systematic review of randomized controlled trials published from June 2000 to February 2012. *Eur. J. Pain* **17**, 158–173 (2013).
47. Goebel, A. *et al.* Complex regional pain syndrome in adults: UK guidelines for diagnosis, referral and management in primary and secondary care. *Royal College of Physicians* [online], https://www.rcplondon.ac.uk/sites/default/files/documents/complex-regional-pain-full-guideline.pdf (2012).
48. Harden, N. Complex regional pain syndrome: treatment guidelines. *RSDSA* [online] www.rsds.org/3/clinical_guidelines (2010).
49. Dworkin, R. H. *et al.* Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin. Proc.* **85** (Suppl.), S3–S14 (2010).
50. Devor, M. in *The Handbook of Clinical Neurology: Pain* 3rd edn Vol. 81 Ch. 19 (eds Cervero, F. & Jensen, T. S.) 261–276 (Elsevier B.V., 2006).
51. Noguchi, K. in *The Handbook of Clinical Neurology: Pain* 3rd edn Vol. 81 Ch. 20 (eds Cervero, F. & Jensen, T. S.) 277–291 (Elsevier B.V., 2006).
52. Puretic, M. B. & Demarin, V. Neuroplasticity mechanisms in the pathophysiology of chronic pain. *Acta Clin. Croat.* **51**, 425–429 (2012).
53. Campero, M., Bostock, H., Baumann, T. K. & Ochoa, J. L. A search for activation of C nociceptors by sympathetic fibers in complex regional pain syndrome. *Clin. Neurophysiol.* **121**, 1072–1079 (2010).
54. Wallace, M. S., Ridgeway, B. M., Leung, A. Y., Gerayli, A. & Yaksh, T. L. Concentration–effect relationship of intravenous lidocaine on the allodynia of complex regional pain syndrome types I and II. *Anesthesiology* **92**, 75–83 (2000).
55. O'Connell, N. E., Wand, B. M., McAuley, J., Marston, L. & Moseley, G. L. Interventions for treating pain and disability in adults with complex regional pain syndrome. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD009416. http://dx.doi.org/10.1002/14651858.CD009416.
56. Torebjörk, E., Wahren, L., Wallin, G., Hallin, R. & Koltzenburg, M. Noradrenaline-evoked pain in neuralgia. *Pain* **63**, 11–20 (1995).
57. Ali, Z. *et al.* Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain. *Pain* **88**, 161–168 (2000).
58. Kingery, W. S. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* **73**, 123–139 (1997).
59. Price, D. D., Long, S., Wilsey, B. & Rafii, A. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional syndrome patients. *Clin. J. Pain* **14**, 216–226 (1998).
60. Rodriguez, R. F. *et al.* Study of the analgesic efficacy of stellate ganglion blockade in the management of the complex regional pain syndrome in patients with pain mediated by sympathetic nervous system: preliminary study. *Rev. Soc. Esp. Dolor* **13**, 230–237 (2006).
61. Stanton, T. R. *et al.* Local anaesthetic sympathetic blockade for complex regional pain syndrome. *Cochrane Database of Systematic Reviews*, Issue. 8. Art. No.: CD004598. http://dx.doi.org/10.1002/14651858.CD004598.pub3.
62. Davis, K. D., Treede, R. D., Raja, S. N., Meyer, R. A. & Campbell, J. N. Topical application of clonidine relieves hyperalgesia in patients with sympathetically maintained pain. *Pain* **47**, 309–317 (1991).
63. Watkins, L. R. & Maier, S. F. Beyond neurons: evidence that immune and glial cells contribute to pathological pain states. *Physiol. Rev.* **82**, 981–1011 (2002).
64. Ludwig, J. & Baron, R. Complex regional pain syndrome: an inflammatory pain condition? *Drug Disc. Today Dis. Mech.* **1**, 449–445 (2004).
65. Cheng, J. K. & Ji, R. R. Intracellular signaling in primary sensory neurons and persistent pain. *Neurochem. Res.* **33**, 1970–1978 (2008).
66. Campana, W. M. Schwann cells: activated peripheral glia and their role in neuropathic pain. *Brain Behav. Immun.* **21**, 522–527 (2007).
67. Huygen, F. J. *et al.* Evidence for local inflammation in complex regional pain syndrome type 1. *Mediators Inflamm.* **11**, 47–51 (2002).
68. Lenz, M. *et al.* Local cytokine changes in complex regional pain syndrome type I (CRPS I) resolve after 6 months. *Pain* **154**, 2142–2149 (2013).
69. Kramer, H. H. *et al.* TNF-α in CRPS and 'normal' trauma—significant differences between tissue and serum. *Pain* **152**, 285–290 (2011).
70. Uceyler, N., Eberle, T., Rolke, R., Birklein, F. & Sommer, C. Differential expression patterns of cytokines in complex regional pain syndrome. *Pain* **132**, 195–205 (2007).
71. Alexander, G. M., van Rijn, M. A., van Hilten, J. J., Perreault, M. J. & Schwartzman, R. J. Changes in cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS. *Pain* **116**, 213–219 (2005).
72. Parkitny, L. *et al.* Inflammation in complex regional pain syndrome: a systematic review and meta-analysis. *Neurology* **80**, 106–117 (2013).
73. Magerl, W., Geldner, G. & Handwerker, H. O. Pain and vascular reflexes in man elicited by prolonged noxious mechano-stimulation. *Pain* **43**, 219–225 (1990).
74. Handwerker, H. O. in *The Handbook of Clinical Neurology: Pain* 3rd edn Vol. 81 Ch. 3 (eds Cervero, F. & Jensen, T. S.) 23–33 (Elsevier B.V., 2006).
75. Leis, S., Weber, M., Isselmann, A., Schmelz, M. & Birklein, F. Substance-P-induced protein extravasation is bilaterally increased in complex regional pain syndrome. *Exp. Neurol.* **183**, 197–204 (2003).
76. Birklein, F., Schmelz, M., Schifter, S. & Weber, M. The important role of neuropeptides in complex regional pain syndrome. *Neurology* **57**, 2179–2184 (2001).
77. Schinkel, C. *et al.* Inflammatory mediators are altered in the acute phase of posttraumatic complex regional pain syndrome. *Clin. J. Pain* **22**, 235–239 (2006).
78. Christensen, K., Jensen, E. M. & Noer, I. The reflex dystrophy syndrome response to treatment with systemic corticosteroids. *Acta Chir. Scand.* **148**, 653–655 (1982).
79. Munts, A. G. *et al.* Efficacy and safety of a single intrathecal methylprednisolone bolus in chronic complex regional pain syndrome. *Eur. J. Pain* **14**, 523–528 (2010).
80. Taskaynatan, M. A., Ozgul, A., Tan, A. K., Dincer, K. & Kalyon, T. A. Bier block with methylprednisolone and lidocaine in CRPS type I: a randomized, double-blinded, placebo-controlled study. *Reg. Anesth. Pain Med.* **29**, 408–412 (2004).
81. Perez, R. S. *et al.* Evidence based guidelines for complex regional pain syndrome type 1. *BMC Neurol.* **10**, 20 (2010).

82. Dirckx, M., Groeneweg, G., Wesseldijk, F., Stronks, D. L. & Huygen, F. J. Report of a preliminary discontinued double-blind, randomized, placebo-controlled trial of the anti-TNF-α chimeric monoclonal antibody infliximab in complex regional pain syndrome. *Pain Pract.* **13**, 633–640 (2013).
83. Perez, R. S. *et al.* The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. *Pain* **102**, 297–307 (2003).
84. Goebel, A. & Blaes, F. Complex regional pain syndrome, prototype of a novel kind of autoimmune disease. *Autoimmun. Rev.* **12**, 682–686 (2013).
85. Goebel, A. *et al.* Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. *Ann. Intern. Med.* **152**, 152–158 (2010).
86. Blaes, F. *et al.* Autoimmune etiology of complex regional pain syndrome (M. Sudeck). *Neurology* **63**, 1734–1736 (2004).
87. Kohr, D. *et al.* Autoimmunity against the β2 adrenergic receptor and muscarinic-2 receptor in complex regional pain syndrome. *Pain* **152**, 2690–2700 (2011).
88. Birklein, F. *et al.* Experimental tissue acidosis leads to increased pain in complex regional pain syndrome (CRPS). *Pain* **87**, 227–234 (2000).
89. Otake, T., Ieshima, H., Ishida, H., Ushigome, Y. & Saito, S. Bone atrophy in complex regional pain syndrome patients measured by microdensitometry. *Can. J. Anaesth.* **45**, 831–838 (1998).
90. Schurmann, M. *et al.* Imaging in early posttraumatic complex regional pain syndrome: a comparison of diagnostic methods. *Clin. J. Pain* **23**, 449–457 (2007).
91. Wuppenhorst, N., Maier, C., Frettloh, J., Pennekamp, W. & Nicolas, V. Sensitivity and specificity of 3-phase bone scintigraphy in the diagnosis of complex regional pain syndrome of the upper extremity. *Clin. J. Pain* **26**, 182–189 (2010).
92. Adami, S., Fossaluzza, V., Gatti, D., Fracassi, E. & Braga, V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann. Rheum. Dis.* **56**, 201–204 (1997).
93. Manicourt, D. H., Brasseur, J. P., Boutsen, Y., Depreseux, G. & Devogelaer, J. P. Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. *Arthritis Rheum.* **50**, 3690–3697 (2004).
94. Varenna, M. *et al.* Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study. *Rheumatology (Oxford)* **52**, 534–542 (2013).
95. Sahin, F., Yilmaz, F., Kotevoglu, N. & Kuran, B. Efficacy of salmon calcitonin in complex regional pain syndrome (type 1) in addition to physical therapy. *Clin. Rheumatol.* **25**, 143–148 (2006).
96. Tran de, Q. H., Duong, S., Bertini, P. & Finlayson, R. J. Treatment of complex regional pain syndrome: a review of the evidence. *Can. J. Anaesth.* **57**, 149–166 (2010).
97. Woolf, C. J. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* **152**, S2–S15 (2011).
98. Baron, R., Hans, G. & Dickenson, A. Peripheral input and its importance for central sensitization. *Ann. Neurol.* (2013).
99. Bauer, C. S. *et al.* The increased trafficking of the calcium channel subunit α2δ-1 to presynaptic terminals in neuropathic pain is inhibited by the α2δ ligand pregabalin. *J. Neurosci.* **29**, 4076–4088 (2009).
100. D'Mello, R. & Dickenson, A. H. Spinal cord mechanisms of pain. *Br. J. Anaesth.* **101**, 8–16 (2008).
101. Sieweke, N., Birklein, F., Riedl, B., Neundorfer, B. & Handwerker, H. O. Patterns of hyperalgesia in complex regional pain syndrome. *Pain* **80**, 171–177 (1999).
102. Maier, C. *et al.* Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* **150**, 439–450 (2010).
103. Pertovaara, A. & Almeida, A. in *The Handbook of Clinical Neurology: Pain* 3rd edn Vol. 81 Ch. 13 (eds Cervero, F. & Jensen, T. S.) 179–192 (Elsevier B.V., 2006).
104. Ossipov, M. H. & Porreca, F. in *The Handbook of Clinical Neurology: Pain* 3rd edn Vol. 81 Ch. 14 (eds Cervero, F. & Jensen, T. S.) 193–210 (Elsevier B. V., 2006).
105. Seifert, F., Kiefer, G., DeCol, R., Schmelz, M. & Maihofner, C. Differential endogenous pain modulation in complex-regional pain syndrome. *Brain* **132**, 788–800 (2009).
106. van de Vusse, A. C., Stomp-van den Berg, S. G., Kessels, A. H. & Weber, W. E. Randomised controlled trial of gabapentin in complex regional pain syndrome type 1 [ISRCTN84121379]. *BMC Neurol.* **4**, 13 (2004).
107. Schwartzman, R. J. *et al.* Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain* **147**, 107–115 (2009).
108. Sigtermans, M. J. *et al.* Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. *Pain* **145**, 304–311 (2009).
109. Finch, P. M., Knudsen, L. & Drummond, P. D. Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. *Pain* **146**, 18–25 (2009).
110. Gustin, S. M. *et al.* NMDA-receptor antagonist and morphine decrease CRPS-pain and cerebral pain representation. *Pain* **151**, 69–76 (2010).
111. Harden, R. N. *et al.* Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. *Pain Med.* **14**, 180–229 (2013).
112. Kemler, M. A. *et al.* Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N. Engl. J. Med.* **343**, 618–624 (2000).
113. Kemler, M. A., De Vet., H. C., Barendse, G. A., Van Den Wildenberg, F. A. & Van Kleef, M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann. Neurol.* **55**, 13–18 (2004).
114. Kemler, M. A., de Vet., H. C., Barendse, G. A., van den Wildenberg, F. A. & van Kleef, M. Effect of spinal cord stimulation for chronic complex regional pain syndrome type I: five-year final follow-up of patients in a randomized controlled trial. *J. Neurosurg.* **108**, 292–298 (2008).
115. Rauck, R. L., Eisenach, J. C., Jackson, K., Young, L. D. & Southern, J. Epidural clonidine treatment for refractory reflex sympathetic dystrophy. *Anesthesiology* **79**, 1163–1169 (1993).
116. Legrain, V., Iannetti, G. D., Plaghki, L. & Mouraux, A. The pain matrix reloaded: a salience detection system for the body. *Prog. Neurobiol.* **93**, 111–124 (2011).
117. Garcia-Larrea, L. & Peyron, R. Pain matrices and neuropathic pain matrices: a review. *Pain* **154** (Suppl. 1), S29–S43 (2013).
118. Cortelli, P., Giannini, G., Favoni, V., Cevoli, S. & Pierangeli, G. Nociception and autonomic nervous system. *Neurol. Sci.* **34** (Suppl. 1), S41–S46 (2013).
119. Jänig, W. Ätiologie und Pathogenese von CRPS. In *CRPS—Complex Regional Pain Syndrome* [German] 1st edn Ch. C (eds Jänig, W. *et al.*) 33–58 (SUVA, 2013).
120. Forderreuther, S., Sailer, U. & Straube, A. Impaired self-perception of the hand in complex regional pain syndrome (CRPS). *Pain* **110**, 756–761 (2004).
121. Sumitani, M. *et al.* Pathologic pain distorts visuospatial perception. *Neurology* **68**, 152–154 (2007).
122. Reinersmann, A. *et al.* Impaired spatial body representation in complex regional pain syndrome type 1 (CRPS I). *Pain* **153**, 2174–2181 (2012).
123. Peltz, E., Seifert, F., Lanz, S., Muller, R. & Maihofner, C. Impaired hand size estimation in CRPS. *J. Pain* **12**, 1095–1101 (2011).
124. Lewis, J. S. & Schweinhardt, P. Perceptions of the painful body: the relationship between body perception disturbance, pain and tactile discrimination in complex regional pain syndrome. *Eur. J. Pain* **16**, 1320–1330 (2012).
125. Maihofner, C., Handwerker, H. O., Neundorfer, B. & Birklein, F. Patterns of cortical reorganization in complex regional pain syndrome. *Neurology* **61**, 1707–1715 (2003).
126. Maihofner, C., Handwerker, H. O., Neundorfer, B. & Birklein, F. Cortical reorganization during recovery from complex regional pain syndrome. *Neurology* **63**, 693–701 (2004).
127. Pleger, B. *et al.* Sensorimotor retuning [corrected] in complex regional pain syndrome parallels pain reduction. *Ann. Neurol.* **57**, 425–429 (2005).
128. Gallace, A., Torta, D. M., Moseley, G. L. & Iannetti, G. D. The analgesic effect of crossing the arms. *Pain* **152**, 1418–1423 (2011).
129. Longo, M. R., Betti, V., Aglioti, S. M. & Haggard, P. Visually induced analgesia: seeing the body reduces pain. *J. Neurosci.* **29**, 12125–12130 (2009).
130. Mancini, F., Longo, M. R., Kammers, M. P. & Haggard, P. Visual distortion of body size modulates pain perception. *Psychol. Sci.* **22**, 325–330 (2011).
131. Mancini, F., Longo, M. R., Canzoneri, E., Vallar, G. & Haggard, P. Changes in cortical oscillations linked to multisensory modulation of nociception. *Eur. J. Neurosci.* **37**, 768–776 (2013).
132. Haggard, P., Iannetti, G. D. & Longo, M. R. Spatial sensory organization and body representation in pain perception. *Curr. Biol.* **23**, R164–R176 (2013).
133. Ramachandran, V. S., Brang, D. & McGeoch, P. D. Size reduction using mirror visual feedback (MVF) reduces phantom pain. *Neurocase* **15**, 357–360 (2009).
134. Moseley, G. L., Parsons, T. J. & Spence, C. Visual distortion of a limb modulates the pain and swelling evoked by movement. *Curr. Biol.* **18**, R1047–R1048 (2008).
135. Lewis, J. S. *et al.* Wherever is my arm? Impaired upper limb position accuracy in complex regional pain syndrome. *Pain* **149**, 463–469 (2010).
136. Bailey, J., Nelson, S., Lewis, J. & McCabe, C. S. Imaging and clinical evidence of sensorimotor problems in CRPS: utilizing novel treatment approaches. *J. Neuroimmune Pharmacol.* **8**, 564–575 (2013).
137. Cohen, H. E. *et al.* Enhanced pain and autonomic responses to ambiguous visual stimuli in chronic complex regional pain syndrome (CRPS) type I. *Eur. J. Pain* **16**, 182–195 (2012).

138. Hall, J. *et al.* Pain and other symptoms of CRPS can be increased by ambiguous visual stimuli—an exploratory study. *Eur. J. Pain* **15**, 17–22 (2011).
139. McCabe, C. S. *et al.* Somatosensory conflicts in complex regional pain syndrome type 1 and fibromyalgia syndrome. *Curr. Rheumatol. Rep.* **11**, 461–465 (2009).
140. McCabe, C. S. & Blake, D. R. Evidence for a mismatch between the brain's movement control system and sensory system as an explanation for some pain-related disorders. *Curr. Pain Headache Rep.* **11**, 104–108 (2007).
141. McCabe, C. S., Haigh, R. C., Halligan, P. W. & Blake, D. R. Simulating sensory–motor incongruence in healthy volunteers: implications for a cortical model of pain. *Rheumatology (Oxford)* **44**, 509–516 (2005).
142. Acerra, N. E. & Moseley, G. L. Dysynchiria: watching the mirror image of the unaffected limb elicits pain on the affected side. *Neurology* **65**, 751–753 (2005).
143. Daly, A. E. & Bialocerkowski, A. E. Does evidence support physiotherapy management of adult complex regional pain syndrome type one? A systematic review. *Eur. J. Pain* **13**, 339–353 (2009).
144. Kemler, M. A., Rijks, C. P. & de Vet., H. C. Which patients with chronic reflex sympathetic dystrophy are most likely to benefit from physical therapy? *J. Manipulative Physiol. Ther.* **24**, 272–278 (2001).
145. Oerlemans, H. M. *et al.* Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type I. *Arch. Phys. Med. Rehabil.* **81**, 49–56 (2000).
146. Severens, J. L. *et al.* Cost-effectiveness analysis of adjuvant physical or occupational therapy for patients with reflex sympathetic dystrophy. *Arch. Phys. Med. Rehabil.* **80**, 1038–1043 (1999).
147. Sherry, D. D., Wallace, C. A., 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* **15**, 218–223 (1999).
148. Harris, A. J. Cortical origin of pathological pain. *Lancet* **354**, 1464–1466 (1999).
149. Sumitani, M. *et al.* Prism adaptation to optical deviation alleviates pathologic pain. *Neurology* **68**, 128–133 (2007).
150. Bultitude, J. H. & Rafal, R. D. Derangement of body representation in complex regional pain syndrome: report of a case treated with mirror and prisms. *Exp. Brain Res.* **204**, 409–418 (2010).
151. Moseley, G. L. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. *Pain* **108**, 192–198 (2004).
152. Moseley, G. L. Graded motor imagery for pathologic pain: a randomized controlled trial. *Neurology* **67**, 2129–2134 (2006).
153. van Hilten, B. J., van de Beek, W. J., Hoff, J. I., Voormolen, J. H. & Delhaas, E. M. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. *N. Engl. J. Med.* **343**, 625–630 (2000).
154. van Rijn, M. A. *et al.* Intrathecal baclofen for dystonia of complex regional pain syndrome. *Pain* **143**, 41–47 (2009).
155. Rommel, O., Malin, J. P., Zenz, M. & Janig, W. Quantitative sensory testing, neurophysiological and psychological examination in patients with complex regional pain syndrome and hemisensory deficits. *Pain* **93**, 279–293 (2001).
156. Monti, D. A., Herring, C. L., Schwartzman, R. J. & Marchese, M. Personality assessment of patients with complex regional pain syndrome type I. *Clin. J. Pain* **14**, 295–302 (1998).
157. Ciccone, D. S., Bandilla, E. B. & Wu, W. Psychological dysfunction in patients with reflex sympathetic dystrophy. *Pain* **71**, 323–333 (1997).
158. DeGood, D. E., Cundiff, G. W., Adams, L. E. & Shutty, M. S. Jr. A psychosocial and behavioral comparison of reflex sympathetic dystrophy, low back pain, and headache patients. *Pain* **54**, 317–322 (1993).
159. Bean, D. J., Johnson, M. H. & Kydd, R. R. Relationships between psychological factors, pain and disability in complex regional pain syndrome and low back pain. *Clin. J. Pain* **30**, 647–653 (2014).
160. de Mos, M. *et al.* Medical history and the onset of complex regional pain syndrome (CRPS). *Pain* **139**, 458–466 (2008).
161. Beerthuizen, A., van 't Spijker, A., Huygen, F. J., Klein, J. & de Wit, R. Is there an association between psychological factors and the complex regional pain syndrome type 1 (CRPS1) in adults? A systematic review. *Pain* **145**, 52–59 (2009).
162. Field, J. & Gardner, F. V. Psychological distress associated with algodystrophy. *J. Hand Surg. Br.* **22**, 100–101 (1997).
163. Puchalski, P. & Zyluk, A. Complex regional pain syndrome type 1 after fractures of the distal radius: a prospective study of the role of psychological factors. *J. Hand Surg. Br.* **30**, 574–580 (2005).
164. Beerthuizen, A. *et al.* The association between psychological factors and the development of complex regional pain syndrome type 1 (CRPS1)—a prospective multicenter study. *Eur. J. Pain* **15**, 971–975 (2011).
165. Bruehl, S. & Carlson, C. R. Predisposing psychological factors in the development of reflex sympathetic dystrophy. A review of the empirical evidence. *Clin. J. Pain* **8**, 287–299 (1992).
166. Bruehl, S. An update on the pathophysiology of complex regional pain syndrome. *Anesthesiology* **113**, 713–725 (2010).
167. Bruehl, S. in *CRPS: Current Diagnosis and Therapy* Vol. 32 Ch. 13 (eds Wilson, P. R. *et al.*) 201–216 (IASP Press, 2005).
168. Lee, B. H. *et al.* Physical therapy and cognitive–behavioral treatment for complex regional pain syndromes. *J. Pediatr.* **141**, 135–140 (2002).

Author contributions

All authors researched the data for the article, provided substantial contributions to discussions of its content, wrote the article and undertook review and/or editing of the manuscript before submission.