Clinical features and pathophysiology of complex regional pain syndrome

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A complex regional pain syndrome (CRPS)—multiple system dysfunction, severe and often chronic pain, and disability—can be triggered by a minor injury, a fact that has fascinated scientists and perplexed clinicians for decades. However, substantial advances across several medical disciplines have recently improved our understanding of CRPS. Compelling evidence implicates biological pathways that underlie aberrant inflammation, vasomotor dysfunction, and maladaptive neuroplasticity in the clinical features of CRPS. Collectively, the evidence points to CRPS being a multifactorial disorder that is associated with an aberrant host response to tissue injury. Variation in susceptibility to perturbed regulation of any of the underlying biological pathways probably accounts for the clinical heterogeneity of CRPS.

Introduction

Complex regional pain syndrome (CRPS) is characterised by pain in combination with sensory, autonomic, trophic, and motor abnormalities. A distinction is made between CRPS-1, in which a nerve lesion cannot be identified, and CRPS-2, in which it can. However, this distinction is not without criticism because bone fracture or surgery will damage peripheral nerve fibres but post-fracture and post-surgical CRPS are almost always classed as CRPS-1. Furthermore, pathological studies on chronic CRPS-1 limbs that have been amputated and skin biopsies of CRPS-1 limbs show degeneration of small (C and Aδ) nerve fibres, which serve nociceptive and autonomic functions. Whether nerve degeneration causes CRPS-1 remains to be established. Additionally, because other causes of neuropathic pain are frequently associated with a loss of C-fibre peripheral terminals, the specificity of these findings with respect to CRPS is questionable.

Our understanding of CRPS has increased substantially in the past decade. Three major pathophysiological pathways have been identified: aberrant inflammatory mechanisms, vasomotor dysfunction, and maladaptive neuroplasticity. The clinical heterogeneity of CRPS is indicative of between-individual variability in the activation of these pathways after tissue injury. Over the past 3–5 years, substantial developments have occurred in several areas of CRPS and their inter-relationships are now being identified; these developments are rapidly changing our understanding of CRPS. In this Review, we present a multidisciplinary overview of CRPS that integrates findings across relevant fields and puts them into perspective. We discuss the clinical and epidemiological features of CRPS and the role of inflammation, vasomotor dysfunction, and maladaptive neuroplasticity in the development and persistence of the disorder.

Clinical presentation and diagnosis

Typically, patients with CRPS present after minor or moderate tissue injury (eg, a wrist fracture). In the acute phase, the injured limb is usually extremely painful, red, warm (although sometimes it quickly becomes cold) and swollen (figure 1A). Other features, which are also confined to the injured limb but not confined to the distribution of a specific nerve or nerve root, include allodynia (whereby usually non-painful stimuli evoke pain) and hyperalgesia (whereby painful stimuli evoke more intense pain than usual), changes in sweating, changes in hair and nail growth, and muscle weakness. In particular, mechanical and thermal hyperalgesia are frequently present in CRPS. As the disorder persists, pain does not subside but often spreads, voluntary motor control is reduced in some patients, hyperpathia might occur, and negative sensory signs (hypoesthesia, hypoalgesia, and hypothermesthesia) can develop. Thus, CRPS seems to be characterised by a mixture of noxious sensations (positive symptoms) and sensory loss (negative symptoms). Over months, the limb often becomes cold (figure 1B). Dystonia (figure 1C), tremor, and myoclonus might also develop. Activity of the limb typically exacerbates signs and symptoms. Over time, clinical features spread proximally (but not distally) and can even emerge on the opposite or ipsilateral limb. In chronic cases with long disease durations (>5 years) other features are sometimes noted, such as urological symptoms, syncope, and even mild cognitive deficits, although the latter is probably not specific to CRPS.

Diagnosis of CRPS is based either on the Orlando criteria, endorsed by the International Association for the Study of Pain, or a modified version called the Budapest criteria (panel), which has higher specificity and also includes motor features of the syndrome. A recent international cohort study confirmed the validity of the Budapest criteria. Diagnosis according to the Budapest criteria is based on the grouping of signs and symptoms into four distinct categories, which were identified by factor analysis. A CRPS severity score to monitor longitudinal changes was subsequently developed.

The feasibility of measuring sensory changes in the diagnosis of CRPS was recently assessed. In a German study in which sensory function was quantitatively assessed in more than 1200 patients who had various neuropathic pain syndromes—including 400 patients with CRPS—and in which data were compared across
diseases and with data from healthy control individuals, patients with CRPS displayed a mixture of gain and loss of sensory function. Gain of sensory function, particularly with respect to thermal and mechanical hyperalgesia, was reported more often in CRPS than in other neuropathic syndromes. However, a unique profile of change in sensory function could not be detected for any of the included neuropathic syndromes and therefore the role of quantitative sensory testing in the diagnosis of CRPS still needs further investigation.

Epidemiology

Incidence of CRPS is unclear. Two population-based studies yielded very different data: 5.5 cases per 100 000 person-years in the USA7 and 26.2 per 100 000 person-years in the Netherlands.8 On the basis of these numbers, one might expect that 20 000–80 000 new cases of CRPS would be identified per year in the USA. Incidence increases with age until 70 years of age, and 3–4 times more women than men are affected.22,23 The arm is affected in about 60% of cases and the leg in about 40%.22 Resolution rate differs greatly between studies, ranging from 74% in the first year23 to 36% within 6 years.23 However, resolution data are difficult to interpret because of heterogeneous study populations, inconsistency in diagnostic rigour, and no consensus on what defines recovery. Fractures (about 45%), sprain (about 18%), and elective surgery (about 12%) are the most frequently reported triggering events.22 Spontaneous-onset CRPS, which presents with a similar clinical picture,25 is uncommon (<10% of cases).22,23 CRPS is often associated with substantial disability, loss of quality of life, and personal and societal economic burden.26,27

Risk factors and prognostic determinants

Nearly everyone experiences tissue trauma, yet few develop CRPS, and the severity of trauma is not linked to the development of CRPS. Clearly, then, some individuals are more susceptible than others. Identification of risk factors other than injury alone might point to underlying biological mechanisms and assist in the development of preventive and treatment strategies. Epidemiological, genetic, and experimental studies have been done in an attempt to identify factors that modulate the risk of developing CRPS and the persistence of the disorder.

Psychological factors

The apparently unpredictable nature of CRPS underpins the popular presumption that a characteristic personality or psychological profile is a key risk factor. Most studies
provide compelling evidence that patients with CRPS are more anxious and depressed than healthy control individuals. However, whether patients with CRPS are more anxious and depressed than patients with other chronic pain syndromes is unclear; available studies report contradictory results, and cross-sectional studies preclude inferences about causality and therefore tell us nothing about susceptibility to the condition. Only a few studies have attempted to obtain accurate information regarding the period before onset of CRPS. The two largest studies showed no evidence of psychological risk factors for CRPS onset. A large population-based case-control study reported no difference in psychological variables between those who developed CRPS after trauma and control individuals without CRPS who were matched for age, sex, and trauma. Another recent prospective multicentre cohort study that included almost 600 consecutive patients with a fracture reported that none of the psychological factors included in the symptom checklist-90 predicted the development of CRPS-1. Clearly, the popular presumption that anxiety and depression predispose to CRPS is incorrect. Whether other psychological factors contribute to the persistence of CRPS remains to be established; research into these topics is ongoing.

Immobilisation of the injured limb
An injured limb is often immobilised, particularly if it is fractured, and early reports suggested that immobilisation might be a risk factor for CRPS. Several characteristic features of CRPS—changes in temperature, mechanosensitivity, and thermosensitivity—can be induced in a healthy limb by immobilisation alone. Healthy volunteers showed mild signs of CRPS, although no pain, after 4 weeks of limb immobilisation. Moreover, after topical application of capsaicin (which induces neurogenic inflammation; see later), mechanosensitivity, thermosensitivity, and perceptual disturbances have been reported in people whose limb was subsequently immobilised for 24 h, but not in people whose limb was not immobilised (Moseley GL, unpublished). The signs rapidly resolved once the limb was moved again. These experimental findings seem consistent with the idea that immobilisation is a risk factor for CRPS.

Epidemiological findings
Results of a large population-based study showed that use of angiotensin-converting-enzyme inhibitors at the time of trauma and a history of migraine or asthma were associated with increased risk of developing CRPS. Migraine was also identified as a risk factor for CRPS in another study. Both of these risk factors implicate inflammation: angiotensin-converting-enzyme inhibitors increase the availability of substance P and bradykinin, which are important mediators of inflammation, and migraine and asthma share an underlying mechanism of neurogenic inflammation with CRPS (see later).

Epidemiological studies have also identified several prognostic variables for CRPS. Although fracture is the most common trigger of CRPS, it is associated with a more favourable course than soft tissue injury. Sex does not seem to affect prognosis in common types of CRPS. However, women have a higher risk of developing a more severe phenotype of CRPS than men: the women-to-men ratio is 5–6 to 1 in those with infections, ulcers, chronic oedema, or marked movement disorders, but 3–4 to 1 in the wider cohort. Finally, those who have cold CRPS, in which impaired thermoregulatory blood flow to the limb leaves it colder than its counterpart, have a worse prognosis than those with warm CRPS, in which excessive vasodilatation in the affected limb leaves it warmer than its counterpart.

All these determinants have been identified on a group level but they are of limited use on an individual level: who will or will not develop CRPS after trauma is still unclear. In a longitudinal study, 1549 nearly consecutive patients who presented with wrist fracture and who were managed non-surgically were assessed within 1 week of their fracture and then followed up 4 months later (Moseley GL, unpublished). A simple assessment of mean pain intensity over the past 2 days, measured on a 0–10 scale, provided high discriminative ability (c index 0.98), such that a mean pain score of over 5 out of 10 over the past 2 days should be classed as a red flag for CRPS.

Genetic findings
CRPS sometimes occurs in several family members and siblings of young-onset cases have an increased risk of developing the syndrome, both of which suggest a potential genetic predisposition to CRPS. Consistent with this possible connection are associations between various CRPS phenotypes and loci in the human genome.
leukocyte antigen region. Genetic studies of CRPS have identified polymorphisms in the tumour necrosis factor alpha (TNFα) gene and the angiotensin-converting-enzyme gene, but there are contrasting findings for the latter. Although a picture of genetic predisposition to CRPS is emerging, associations have so far not been replicated in independent studies, and because of small sample sizes the possibility of false-positive findings cannot be excluded. Nonetheless, epidemiological and genetic findings suggest that aspects of the individual’s response to tissue injury are important in the development of CRPS.

**The role of inflammation**

Findings from in-vivo experiments in man show that even minor tissue trauma is sufficient to amplify cytokine signalling in the traumatised tissue. Cytokines and nerve growth factor can excite nociceptors and induce long-term peripheral sensitisation. Moreover, findings from in-vitro experiments suggest that cytokines and nerve growth factor enhance the release of inflammatory neuropeptides in primary afferent neurons. The activation of cutaneous nociceptors can induce retrograde depolarisation of small-diameter primary afferents (axon reflex), causing the release of neuropeptides such as substance P and calcitonin-gene-related peptide (CGRP) from sensory terminals in the skin. These neuropeptides evoke vasodilation and protein extravasation in the tissue, and the resulting signs (reddening, warming, and oedema) are called neurogenic inflammation.

Most post-traumatic inflammatory changes that occur in CRPS are mediated by CGRP and substance P. Serum concentrations of CGRP and substance P are higher in patients with CRPS than in healthy control individuals. Elevated CGRP release is probably responsible for the augmented flare response in patients with CRPS, as quantified by laser doppler measurement of skin perfusion. Although C fibres usually contain too little substance P to generate electrically evoked extravasation, substantial protein extravasation occurs in the affected limb of patients with CRPS. Unlike the increased flare response, which occurs experimentally in both unaffected and affected limbs in patients with CRPS, increased protein extravasation is limited to the affected limb.

The most likely mechanism underpinning facilitated neurogenic inflammation in CRPS is post-junctional signalling caused by hampered inactivation of neuropeptides or increased receptor availability. When substance P was perfused through dermal microdialysis fibres, it produced greater extravasation in both the affected and the unaffected limbs of patients with CRPS than it did in control individuals. Increased substance P signalling might also account for the increased cytokine expression seen in CRPS: substance P stimulates keratinocytes to express cytokines in vitro and skin biopsies from CRPS-affected limbs in both rats and human beings showed increased substance P receptor immunostaining in keratinocytes (figure 2). These findings support the hypothesis that facilitated cutaneous neuropeptide signalling contributes directly to the enhanced extravasation, limb oedema, and increased cytokine expression that are present in CRPS. However, the way in which the immune and nervous systems interact—particularly in the bones, muscles, and connective tissue—is still not fully understood and warrants further research.

Concentrations of TNFα and interleukin-6 in blister fluid are greater in the CRPS-affected limb than the unaffected one, and this difference only gradually resolves during the 6 years after injury. In serum, concentrations of soluble TNF receptors and the pro-inflammatory cytokines TNF, interleukin-1, and interleukin-8 are increased in early CRPS (mean 3 months), whereas anti-inflammatory cytokines such as interleukin-4, interleukin-10, and transforming growth factor-β1 are decreased. These cytokine changes in blister fluid and serum are not linked to clinical signs or to disease duration, but they are associated with the extent of mechanical hyperalgesia. Because mechanical hyperalgesia is a hallmark of central sensitisation—a process by which the excitability of neurons in the spinal cord is increased—anti-inflammatory cytokines probably act not only locally in the limb but also in the spinal cord, most likely by sensitisation of secondary nociceptive neurons or by glial–neuronal interaction. Another recent study supported immune system involvement in CRPS. Findings in patients with longstanding CRPS showed that, although the total monocyte count was not altered, the percentage of the proinflammatory CD14+CD16+ monocyte/macrophage subgroup was raised compared with healthy control individuals matched for age and sex. Individuals with a high percentage of CD14+CD16+ monocytes also had significantly lower plasma concentrations of the anti-inflammatory cytokine interleukin-10, which supports our previous finding. In view of the cross-sectional nature of these studies, whether immune changes were already present before CRPS (in which case they might have facilitated onset of CRPS) or after developing CRPS (in which case they might have played a part in the maintenance of the syndrome) remains unclear. The assumption that central sensitisation by inflammatory cytokines might contribute to pain in CRPS is supported by findings that show increased interleukin-1β and interleukin-6 cytokine concentrations in spinal fluid from patients with chronic CRPS (mean symptom duration 7–8 years). However, these findings were not confirmed in another study that assessed cytokine concentrations in spinal fluid of patients with CRPS characterised by dystonia, suggesting that further research in this field is needed.
The aberrant inflammatory response to tissue injury reported in CRPS does not seem to be caused by a cellular-mediated immune response. Sedimentation rates, antigen titres, autoimmune antibody concentrations, lymphocyte populations, activated T-cell concentrations, and blood cell counts are all normal. Moreover, histological studies show little or no inflammatory cell infiltrate in patients with CRPS.5,59,77

Autoimmune mechanisms might be involved in the pathophysiology of CRPS. About 35% of patients with CRPS have surface-binding autoantibodies against sympathetic and mesenteric plexus neurons and differentiated cholinergic type neuroblastoma cell lines.78,79 Findings from a recent study suggest that the antigens for these autoantibodies might be α-adrenoceptors and muscarinergic acetylcholine receptors (Birklein F, unpublished). However, the significance of these findings is unclear because most patients do not have clinical evidence of generalised autonomic failure that can be attributed to autoimmune serum antibody involvement. Clearly further work is needed.

The role of vasomotor dysfunction

Vasomotor dysfunction is common in CRPS.80 The affected limb is usually warmer than the healthy limb early on, and colder than the healthy limb later on. This shift in temperature suggests that the activity in vasoconstrictor neurons changes over time in CRPS. This temperature shift has been investigated experimentally with central sympathetic vasoconstrictor reflexes induced by whole-body warming and cooling, and by respiratory stimuli.81,82 Three distinct patterns of temperature change were identified in people with CRPS. The first was a warm type, in which the affected limb was warmer and skin perfusion values were higher than the contralateral limb, and occurred in patients who had had CRPS for a mean of 4 months. Even substantial body cooling failed to activate sympathetic vasoconstrictor neurons.82 Norepinephrine concentrations from the venous effluent above the painful area were lower in the affected limb than in the contralateral one.82 The second pattern was an intermediate type, in which temperature and perfusion were either warmer or colder, depending on the amount of sympathetic activity. This pattern occurred in patients with a mean disease duration of 15 months. The third pattern was a cold type, in which temperature and perfusion in the affected limb were consistently lower than those in the contralateral limb, and occurred in patients who had had CRPS for a mean of 28 months. However, paradoxically, norepinephrine concentrations were also lower on the affected side.82 These data suggest that, in addition to the aforementioned inflammatory vasodilatation, CRPS is associated with a unilateral inhibition of cutaneous sympathetic vasoconstrictor neurons, which leads to a warmer limb in the acute stage. This thermoregulatory impairment is probably caused by functional changes in the spinal cord, brainstem, or brain that are triggered by the initial trauma. There are suggestions that cutaneous sympathetic vasoconstrictor activity returns to normal as CRPS persists,82 even though the limb becomes cold and bluish. Biopsies taken from people with chronic CRPS-1 suggest that this apparent paradox is probably explained by increased density or responsiveness of α-adrenergic receptors in the skin.83,84 Thus, although central disturbances in efferent sympathetic outflow seem to be predominant in the acute stage of CRPS, disturbed neurovascular transmission and development of hyper-reactivity of blood vessels to circulating catecholamines seem to predominate in the chronic stage. However, not all CRPS cases pass through these different stages that are defined by skin temperature. About 20% of patients with CRPS have the cold type from the start. These patients not only differ in skin temperature but also in sensory symptoms and history.85

The sympathetic nervous system, in addition to its effect on peripheral circulation in CRPS, might also contribute to pain. Clinical studies in patients with CRPS support the idea that nociceptors develop catecholamine sensitivity,86,87 probably as a result of decreased activity of

![Figure 2: Fluorescence photomicrographs of NK1 receptor expression in keratinocytes from a patient with CRPS](image-url)
cutaneous sympathetic vasoconstrictor neurons. Norepinephrine released by the sympathetic nerve fibres might activate or sensitise the altered afferent neurons. This sympathetic–afferent coupling forms the theoretical basis for the clinical phenomenon of sympathetically maintained pain.89 In a study of patients with CRPS-1 in which cutaneous sympathetic vasoconstrictor outflow to the painful limb was activated to the highest possible physiological level by whole-body cooling,89 the intensity and area of spontaneous pain and mechanical hyperalgesia increased significantly in patients who were classed as having sympathetically maintained pain (defined by pain reduction with sympathetic blocks) but not in patients with sympathetically independent pain. In addition to a coupling in the skin, a sympathetic–afferent interaction probably also occurs in tissues of the deep somatic domain, such as bones, muscles, or joints. However, one study suggested that in some patients arousal of sympathetic activity might still result in pain even after successful sympathetic blockade, which suggests that a central process—indeed, much of the peripheral sympathetic nervous system—cannot be completely ruled out in all patients.90

Changes in the endothelium might also play a part in impaired peripheral circulation in chronic CRPS. Endothelial dysfunction is associated with a decreased ability to release endothelial nitric oxide, which leads to sustained vasoconstriction. Decreased concentrations of nitric oxide have been noted in CRPS, both directly (impaired concentrations of nitric oxide in suction blister fluid of the affected compared with the unaffected side)90 and indirectly (impaired acetylcholine-induced vaso-dilation of the affected compared with the unaffected side and compared with control individuals).91 However, whether these changes are important in the development of CRPS or are a consequence of the trophic changes that affect the skin, muscles, and bones in people with CRPS is unclear.

The role of the CNS
The CNS undergoes functional and structural changes in people with persistent pain and these changes are thought to be particularly important in CRPS.92 These persistent changes in the CNS lead to central sensitisation.93 The mechanisms of central sensitisation are not completely understood but might involve disinhibition of spinal and trigeminal nociceptive neurons or facilitation of nociceptive activity by excitatory neurons that project from the rostroventral medulla.94 Similar changes occur in structures involved in the emotional aspects of pain, such as the amygdala, anterior cingulate gyrus, and prefrontal cortex,95,96 and these changes might represent a substrate for long-term cognitive and mood changes that are learned and retained—eg, conditioned fear and addictive behaviour.97 The sensitising process seems to distort or suppress non-noxious sensations. Loss of an inhibitory influence of normal cutaneous sensations in the CRPS-affected limb might enhance the excitability of thalamocortical nociceptive networks, thereby creating a vicious circle.98,99 One key event in central sensitisation is the activation and upregulation of glutamate receptors, which enhance signal transmission in the nociceptive circuitry from the spinal cord to the cerebral cortex,100 that is, sensitised spinal nociceptive neurons become more responsive to peripheral input and might even fire in the absence of such input. As such, central sensitisation can cause chronic pain, hyperalgesia, and allodynia, as well as the spreading of pain to adjacent non-injured areas.99 Thus, antagonists of, for example, the NMDA receptor, are expected to induce analgesia in CRPS. Intravenous infusion of the NMDA receptor antagonist ketamine over several days caused a clinically significant reduction in pain for 11 weeks in patients with CRPS.101 This long-lasting analgesic effect in CRPS suggests that ketamine causes long-term desensitisation of the NMDA receptor or, at least, an as yet unspecified NMDA-mediated downstream process.102

A potentially important mechanism, hyperalgesic priming, might explain why in some patients a transient insult can lead to chronic pain: according to this theory, a transient insult triggers long-lasting changes in primary afferent nociceptors that prime them to become hyper-responsive to future mild insults that would normally not evoke pain in the unprimed state.103 The epsilon isoform of protein kinase C in the primary afferent nociceptor plays multiple crucial parts in this phenomenon.104 Although the cellular mechanisms of hyperalgesic priming occur within the peripheral terminals of primary afferent nociceptors, the resultant abnormal afferent activity can trigger plastic changes in the CNS. Emerging evidence suggests that hyperalgesic priming might be not only a basic pathophysiological mechanism of chronic re-injury pain, but might also be key to understanding some of the most perplexing chronic pain conditions, including pain syndromes that are stress related (eg, fibromyalgia, irritable bowel syndrome, or post-traumatic stress disorder), and neuropathic (eg, associated with diabetes, chemotherapy for cancer, or AIDS).105

Another manifestation of CNS dysfunction in CRPS is impaired motor function. Impaired motor function is common after most injuries but generally resolves as the patient recovers. However, in CRPS susceptible patients develop marked movement disorders. Dystonia, the most prevalent movement disorder in CRPS, is characterised in the arm by persistent flexion postures of the fingers and wrist and in the leg by plantar flexion and inversion of the foot, with or without clawing of the toes (figure 1C).106 The onset of dystonia occurs after the acute stage, which suggests that it is not caused by acute inflammatory mechanisms.46 The risk of dystonia spreading to additional limbs in patients with CRPS increases with the number of limbs that are already dystonic.46 This accelerated disease course is a typical
characteristic of maladaptive neuronal plasticity.\textsuperscript{40,106} Dystonia does not respond to intravenous ketamine, which suggests that neuroplastic changes have occurred that are distinct from those associated with sensitisation. Central sensitisation is an important neurophysiological characteristic in patients with CRPS whether or not they have dystonia, which suggests that the mechanisms underpinning dystonia occur over and above central sensitisation.\textsuperscript{107–110} The nature of these mechanisms is not well understood, but enhancement of spinal inhibitory neurotransmission by intrathecal administration of the GABA type B receptor (GABAB) agonist baclofen, but not glycine, improved dystonia in patients with CRPS.\textsuperscript{111,112} Thus, spinally mediated GABAergic mechanisms probably play a specific part in the dystonia associated with CRPS.\textsuperscript{111,112}

There is accumulating evidence that supraspinal mechanisms are also involved in the pathophysiology of CRPS.\textsuperscript{113} For example, in a healthy participant, repetitive noxious electrical stimulation on the back of the hand will induce adaptation to the stimuli, such that the pain evoked by the stimuli is reduced, indicative of descending inhibition, and they will develop an area of hyperalgesia, indicative of descending facilitation. However, patients with CRPS adapt less to such stimuli, regardless of whether they are stimulated on the affected hand or the unaffected hand, and develop a larger area of hyperalgesia.\textsuperscript{114} These data suggest that descending inhibition is reduced and descending facilitation augmented in patients with CRPS.

Maladaptive changes have also been noted in higher order cognitive representations in patients with CRPS. People with longstanding CRPS tend to perceive their affected limb to be larger than it really is.\textsuperscript{115} They also report distortions of the mental image of their limb—eg, missing components or alterations in shape, posture, and temperature of the whole limb or of discrete parts of the limb.\textsuperscript{116} They can report feelings of hostility or disgust towards the affected limb, or feel as though it is a separate entity, a foreign body that they would like to have amputated.\textsuperscript{116} Two studies support the notion that these higher order disturbances are not simply a consequence of having CRPS, but might in fact exert a top-down effect on the limb itself. The first study showed that two cardinal signs of CRPS—limb-specific disruption of temperature control and tactile dysfunction—can be evoked experimentally in healthy volunteers by inducing an illusion of disownership of that limb.\textsuperscript{117} The second study showed that the swelling and pain evoked by movement of the CRPS-affected limb is more severe if patients view a magnified image of the limb; if it looked bigger, it hurt more and became more swollen.\textsuperscript{118} Experimentally induced pain in healthy volunteers is decreased when the view of the limb is magnified,\textsuperscript{119} further pointing to cortical maladaptation in CRPS.

The perceptual disturbances that are common in CRPS are similar to disturbances associated with unilateral neglect after stroke.\textsuperscript{120,121} Several other phenomena are common to both conditions. First, patients can perceive touch on the affected limb if they watch the mirror image of the unaffected limb being touched.\textsuperscript{122} Second, patients perform poorly on tasks in which they are required to judge the laterality of a pictured limb.\textsuperscript{123} Third, patients show a bias in tactile processing away from the affected side rather than the affected limb,\textsuperscript{124} that is, when patients cross their limbs, tactile input from the affected limb, now on the unaffected side of the midline, is prioritised over that from the unaffected limb, now held in the affected side of space. Moreover, the extent of this bias in tactile processing away from the affected side is positively associated with the extent of cooling of the affected limb compared with the unaffected one. Recent work has suggested that cold-type CRPS is associated with a cold side of space—ie, crossing the arms so that the healthy hand is on the affected side of the midline reduces the temperature of the healthy hand (Moseley GL, unpublished). The idea that maps in the brain of external space can influence thermal regulation is consistent...
with the recent suggestion of a cortical body matrix, which integrates somatotopic and spatial representations, the sense of ownership, and homoeostatic regulation of the body. Patients with CRPS might have ipsilateral hemisensory impairment, and the neglect syndrome is characterised by hemisensory impairment. However, patients with CRPS, unlike those with spatial neglect, are always aware of their altered feelings towards the limb and perform normally on clinical tasks, such as the line bisection test. They invariably state that although they believe that the limb is theirs, they feel as though it is not. This finding suggests that the neglect-like disturbances reported in CRPS are a result of an implicit mechanism to avoid provocation of pain or an altered representation of aspects of the limb, rather than a direct consequence of actual neural damage.

In line with these clinical findings, functional imaging techniques have shown a substantial reorganisation of the somatotopic map within the primary somatosensory cortex (S1) contralateral to the affected limb in patients with CRPS. The S1 representation of the affected hand was smaller than that of the opposite hand, and the S1 representation of the hand shifted towards the ipsilateral mouth. The extent of these changes is associated with spontaneous CRPS pain and mechanical hyperalgesia. When CRPS symptoms decreased after treatment, this S1 cortical reorganisation also reversed (figure 3). This cortical reorganisation might explain some of the puzzling clinical signs of CRPS; for example, the spatial distribution of sensory disturbances in a glove-like or stocking-like pattern, the occurrence of tactile-induced referred sensations, the perception that the limb is bigger than it really is, and the presence of hemisensory deficits.

Cortical changes also affect the primary motor cortex in patients with CRPS. Results from a transcranial magnetic stimulation study revealed decreased inhibitory mechanisms and increased excitability in the contralateral primary motor cortex of patients with CRPS. Abnormalities of inhibitory mechanisms were also noted in the ipsilateral motor cortex of patients with CRPS, which is consistent with reports of slight preclinical motor impairment of the unaffected limb. Furthermore, bilateral cortical changes suggest a widespread impairment of central motor processing in CRPS. Findings from an fMRI study on cortical activation during tapping movements of the CRPS-affected hand showed that patients with CRPS had substantial reorganisation of central motor circuits, with greater activation of primary motor and supplementary motor cortices than control individuals undertaking the same task. Furthermore, there was increased activation of the ipsilateral motor cortex, and the magnitude of motor dysfunction correlated with activation of the posterior parietal cortices, supplementary motor cortex, and primary motor cortex. Clearly, there are widespread changes in cortical function in people with CRPS, and, although the exact role of these changes in the pathophysiology of CRPS has not been elucidated, they probably contribute to the motor and sensory impairments that are commonly seen in CRPS.
Conclusions
Epidemiological, genetic, and experimental studies suggest that the pathophysiology of CRPS is multifactorial in nature and is characterised by an aberrant host response to tissue injury. We propose that (neurogenic) inflammation, nociceptive sensitisation, vasomotor dysfunction, and maladaptive neuroplasticity account for most or all of the clinical features of CRPS (figure 4). Interindividual differences in the extent to which these mechanisms are affected account for the clinical heterogeneity of the disorder. We argue that the responsible mechanisms can be conceptualised as a framework, each component of which should be considered in the management of these patients; that is, each of these components should be assessed, diagnosed, and monitored. Finally, consideration of the multiple mechanisms implicated in the pathophysiology of CRPS should provide a basis for biomarker discovery and more targeted therapeutic interventions.

Contributors
JM and JJvH designed, organised, and undertook the literature review. All authors were involved in writing the first draft and reviewed and critiqued the manuscript.

Conflicts of interest
FB has received fees as consultant, speaker, or both from Pfizer, Grünenthal, Eli Lilly, MedUpdate, and GlaxoSmithKline, and for expert testimony for Shire. RB has received grants or research support from Pfizer, Genzyme, and Grünenthal, is a member of the IMI "European" collaboration (industry members AstraZeneca, Pfizer, Esteve, UCB Pharma, Sanofi-Aventis, Grünenthal, Eli Lilly, Neuroscience Technologies, and Boehringer Ingelheim), and has received fees as consultant, speaker, or both from Pfizer, Genzyme, Grünenthal, Mundipharma, Allergan, Sanofi Pasteur-Meditecnic, Eisai, UCB, Eli Lilly, Boehringer Ingelheim, Astellas, and Novartis. CM has received fees as a consultant, speaker, or both from Pfizer, Biomorica, Allergan, and Grünenthal. JJvH has received fees as consultant and speaker from Medtronic, GlaxoSmithKline, and Novartis. All other authors declared that they have no conflicts of interest.

Acknowledgments
JM and JJvH participate in TREND, a Dutch knowledge consortium funded by the Netherlands’ Ministry of Economic Affairs (BSR903016). GLM is supported by and receives project funding from the National Health and Medical Research Council of Australia (IDs 571090, 630431, 63136, and 100817). FB is supported by the Rhineland Palatinate Foundation of Innovation (Project 936) and the Deutsche Forschungsgemeinschaft (Graduiertenkolleg Neuwissenschaften Mainz). RB receives funding from the German Federal Ministry of Education and Research and the German Research Foundation (DFG). CM receives funding from the German Research Network “Neuropathic Pain” (Federal Ministry of Education and Research [BMBI]) and the German Research Foundation (DFG; Klinische Forschergruppe 130). WSK receives funding from the Department of Veteran Affairs, Rehabilitation Research and Development Service (Grant F7137R).

References


29 Bruehl S. Do psychological factors play a role in the onset and maintenance of CRPS? Complex regional pain syndrome. Pain 2001; 87: 275–82.


