# Review of complex regional pain syndrome and the role of the neuroimmune axis

Amrita Prasad, MD[1] [ORCID] and Krishnan Chakravarthy, MD[2,3]

## Abstract

**Background:** Complex regional pain syndrome (CRPS) is a progressive and painful disease of the extremities that is characterized by continuous pain inconsistent with the initial trauma. CRPS is caused by a multi-mechanism process that involves both the peripheral and central nervous system, with a prominent role of inflammation in CRPS pathophysiology. This review examines what is currently known about the CRPS inflammatory and pain mechanisms, as well as the possible impact of neurostimulation therapies on the neuroimmune axis of CRPS.

**Study design:** A narrative review of preclinical and clinical studies provided an overview of the pain and inflammatory mechanisms in CRPS and addressed the effect of neurostimulation on immunomodulation.

**Methods:** A systematic literature search was conducted based on the PRISMA guidelines between September 2015 to September 2020. Data sources included relevant literature identified through searches of PubMed, Embase and the Cochrane Database of Systematic Reviews.

**Results:** Sixteen preclinical and eight clinical studies were reviewed. Preclinical studies identified different mechanisms of pain development in the acute and chronic CRPS phases. Several preclinical and clinical studies investigating inflammatory mechanisms, autoimmunity, and genetic profiles in CRPS, supported a role of neuroinflammation in the pathophysiology of CRPS. The immunomodulatory effects of neurostimulation therapy is still unclear, despite clinical improvement in the CRPS patients.

**Conclusions:** Increasing evidence supports a role for inflammation and neuroinflammation in CRPS pathophysiology. Preliminary neurostimulation findings, together with the role of (neuro)inflammation in CRPS, seems to provide a compelling rationale for its use in CRPS pain treatment. The possible immunomodulatory effects of neurostimulation opens new therapeutic possibilities, however further research is needed to gain a better understanding of the working mechanisms.

## Introduction

Complex regional pain syndrome (CRPS) is a progressive and painful disease of the extremities that can develop as a result of trauma (e.g. soft tissue trauma, fracture) or surgery, although spontaneous onset has also been described in 3–11% of cases.[1–4] The presence of autonomic dysfunction, persistent regional inflammatory changes, and a lack of dermatomal distribution makes it distinct from other pain syndromes.[4] The disease is characterized by continuous pain that is inconsistent with the initial trauma, and if left untreated or inadequately treated, the disease progression can severely limit the patient's quality of life.[5,6] The incidence rate of CRPS varies between 5.46 to 26.2 per 1,00,000

[1]Axxon Pain, Brisbane Private Hospital, 259 Wickham Terrace, Brisbane, Queensland 4000, Australia
[2]Division of Pain Medicine, Department of Anesthesiology, University of California San Diego, La Jolla, CA, USA
[3]Department of Anesthesiology and Pain Medicine, VA San Diego Health Care, San Diego, CA, USA

**Corresponding Author:**
Amrita Prasad MD, Axxon Pain, Brisbane Private Hospital, 259 Wickham Terrace, Brisbane, Queensland 4000, Australia.
Email: a.prasad@live.com.au

person-years with a prevalence of 10.57 per 1,00,000, and women are reported to be more affected than men.[1,2] Ott et al. reported a higher prevalence in women 71% vs 29% in males in a population of 1043 patients with CRPS. They also reported that CRPS has a higher propensity to affect the upper extremity (70% of patients), with CRPS I occurring in 88% of patients versus 12% in CRPS II.[7]

Kim et al. reported that the incidence of CRPS in Korea was 29.0 per 1,00,000 person years in 2015 with an increasing trend, which correlated with patient age in the 70 s and female sex, and the majority (63%) being CRPS I compared with 37% CRPS II.[8]

The pathophysiology of CRPS is not completely understood, however, recently it has been agreed that CRPS is caused by a multifactorial process that involves both the peripheral and central nervous system.[9,10] Several pathophysiology mechanisms are involved in the development of CRPS, such as inflammation, peripheral and central sensitization, circulating catecholamines, altered sympathetic nervous system and cutaneous innervation, brain plasticity, genetic factors, and psychologic factors which makes treatment extremely challenging.[11,12] It is currently unclear how all of these mechanisms interact in the development of CRPS, however, it appears as if inflammation has a cardinal role.[13]

Conventional treatment for CRPS includes physiotherapy and pharmacological treatment with a variety of drugs (corticosteroids, pain medication, nonsteroidal anti-inflammatory drugs, sympathetic block), however many patients fail to experience clinically meaningful pain relief from these treatments alone.[14–19] Furthermore, chronic CRPS patients who experience drug resistance, loss of treatment efficacy or those who become resistant to drug therapy may be treated with specialized immunomodulatory medication (anti-TNF-alpha or immunoglobulins)[20,21] or with neuromodulation treatment strategies.

Conventional spinal cord stimulation (SCS) has shown strong evidence for the treatment of chronic pain disorders as well as for CRPS, whereas newer waveforms and novel ultra-high frequencies may provide an even greater likelihood of pain relief.[22] Comparably, moderate-level evidence supports dorsal root ganglion stimulation (DRGS), which represents an anatomically targeted approach for the treatment of neuropathic pain conditions and CRPS.[23] Some studies have even reported superiority of DRGS over conventional SCS in a variety of pain disorders.[24–28] Although these neuromodulation therapies has shown strong evidence of pain relief in chronic pain and CRPS, the precise mechanisms of these treatment modalities are poorly understood.[29–32] Possible relationships between neurostimulation pain therapies, its effect on the immune system and the inflammatory component of CRPS, still remain relatively unexplored in preclinical and clinical studies.

Therefore, the aim of this narrative review was to provide a current overview of the pain and inflammatory mechanisms in CRPS, identified in both preclinical and clinical CRPS studies, and to assess the effect of neurostimulation on immunomodulation.

## Methods

### Search strategy and selection criteria

A systematic literature search was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[33] to select appropriate literature for this narrative review. On 14 September 2020, a comprehensive literature search was conducted to generate a list of study abstracts for screening. The search included the electronic databases PubMed/MEDLINE, Embase, and the Cochrane Database of Systematic Reviews. Titles and abstracts of publications in the aforementioned databases were searched for the following terms: "complex regional pain syndrome", "CRPS", "immune", "immunomodulation", "neuroimmune", "inflammation", "dorsal root ganglion", "DRG", "spinal cord stimulation", "SCS", "neuromodulation", "chronic pain", and "neuropathic pain". The literature search encompassed 01 September 2015 to 01 September 2020, which the authors believed would provide a sufficient overview of the current literature.

### Study eligibility and inclusion criteria

Both animal and human CRPS studies, who investigated pain and inflammatory mechanisms of the disease and/ or who identified biomarkers in response to the therapeutic intervention of SCS or DRG stimulation, were included. Studies were excluded if they were not published in a peer-reviewed journal or book and if not available in English. Conference abstracts, presentations and posters were also excluded. A reviewer worked independently to identify original studies eligible for further review by screening abstracts and titles. If a study was determined to be relevant, the full-text manuscript was obtained and reviewed.

## Complex regional pain syndrome

### Subtypes and phenotypes

CRPS has been divided into two clinical subtypes, type I and II. CRPS type II develops after major nerve damage, whereas patients with no demonstrable nerve lesion is classified as CRPS type I.[4,34] The latter

subtype is more common than the former.[5] Despite these different subtypes, patients seem not to differ in clinical symptoms and signs, nor in their response to therapy.[9] Moreover, a recent study suggested two further subtypes based on the observed signs and symptoms portrayed by patients: 'warm' CRPS and 'cold' CRPS.[35] The warm subtype is characterized with a more inflammatory phenotype with a warm, red, edematous, and sweaty extremity, whereas the cold subtype is associated with colder temperatures, blue or pale skin, and a lees edematous extremity.

## Pathophysiology

The pathophysiology of CRPS is still controversial, however recently there has been an agreement that CRPS is caused by a multifactorial process that involves both the peripheral and central nervous system.[9] Several mechanisms have been implicated in the development of CRPS, namely: inflammation, altered cutaneous innervation, sympathetic nervous system, changes in circulating catecholamines, autoimmunity, brain plasticity, genetic effects and psychological influences.[13,36] Nonetheless, it is not yet clear how and to what extent these mechanisms cause and maintain CRPS.

Most commonly, after initial peripheral limb trauma, a person can experience signs of inflammation, such as heat, pain, redness and swelling.[37] This inflammatory response is a normal, post-traumatic physiological response. However, in CRPS patients, this inflammation process is exaggerated and primary afferent sensory neurons release increased amounts of neuropeptides.[34,38,39] This increased release of neuropeptides (calcitonin gene-related peptide and substance P and bradykinin) in CRPS can lead to varying degrees of persistent edema, vasodilation, temperature changes and probably hyperhidrosis.[34,40] This points toward facilitated neurogenic inflammation in CRPS.

Concurrently, inflammatory mediators (e.g., cytokines), growth factors, catecholamines and autoantibodies are thought to contribute to trophic changes (e.g., activation of keratinocytes, fibroblasts or osteocytes) and sensitize peripheral nociceptors in the affected limb.[34,41] Consequently, this can induce phenomena such as movement-related pain and heat hyperalgesia. Some mediators (e.g., growth factors, cytokines and centrally released neuropeptides from primary afferents) can also sensitize second-order neurons in the spinal cord, resulting in both skin and deep-tissue hyperalgesia and allodynia. If CRPS is treated unsuccessfully during this inflammatory phase, the prolonged inflammation and nociceptive activity could lead to peripheral nerve damage, causing loss of function and cortical reorganization of the brain in some patients.[34,42] Associated symptoms are non-dermatomal sensory deficits,

disturbances of the body perception, neglect-like phenomena, motor symptoms like dystonia or tremor and central sympathetic changes leading to the cold skin.[34,43]

Apart from the neurogenic inflammation, recent studies have also provided supporting evidence for a role of neuroinflammation in CRPS.[44,45] Neuroinflammation refers to inflammation that occurs within the central/peripheral nervous system which is primarily characterized by glial cell activation that can further lead to the increased production of chemokines and pro-inflammatory cytokines.[46] Furthermore, it has been suggested that neuroinflammation can be caused by increased neuronal activity of primary afferent nerve fibers and/or higher-order neurons.[46,47] Neuroinflammation could also be responsible for the transition from acute to chronic pain as well as for the maintenance of chronic pain in CRPS.[46]

## Current concepts in preclinical and clinical studies

Based on the ongoing understanding of CRPS pathophysiology, the following section will provide an overview of current findings regarding the CRPS mechanisms and potential treatment targets identified from preclinical (n = 16) and clinical (n = 8) CRPS studies (Table 1). Included preclinical CRPS studies mainly

**Table 1.** Summary of molecular and cellular mechanisms that may contribute to CRPS.

| Mechanism | Supporting pattern of findings |
|---|---|
| Inflammatory factors | Increased proinflammatory cytokines, including TNF-$\alpha$, MPO, NAGase,[47] and interleukin-1 in CRPS[49] |
| | Reduced anti-inflammatory cytokines including interleukin-10[64] |
| | Increased systemic levels of proinflammatory neuropeptides including CGRP, substance P,[66] and bradykinin[52] |
| | Glial cell activation and central sensitization[60–63] |
| Autoimmunity | Altered T cell system, Th17, Tregs and CD39 may be critical to the inflammatory activation seen in CRPS patients[54–57] |
| | Increased plasma T lymphocytes CD4+ and CD8+[56] and level of T cell activity in CRPS[54–57] |
| | Animal post fracture model of CRPS found that IgM protein levels were elevated, and their serum had pronociceptive effects[68] |
| Genetic factors | ERK1/2 cascade suggested to play a crucial role in mediating pain[72–74] |
| | Cerebral expression of NF$\kappa$B may have implications for CRPS[75] |

TNF, tumor necrosis factor; CGRP, calcitonin gene related peptide; MPO, myeloperoxidase; NaGase, N-acetyl-$\beta$-?-glucosaminidase; NF$\kappa$, nuclear factor kappa; ERK, extracellular signal regulated kinase.

used one of two different models, namely the chronic post-ischemic pain (CPIP) or tibia fracture model (TFM). Both models develop CRPS-like symptoms which last for up to 4 weeks and 5 months, respectively.[48]

## Inflammatory and pain mechanisms

CRPS type I is commonly caused by ischemia/reperfusion injury, which also forms the basis for CRPS induction in the CPIP model.[49,50] Consequently, the CPIP model has been used to investigate the mechanisms/mediators involved in CRPS-related pain and inflammation, as well as the effectiveness of treatment compounds for these mediators.[49,50] In a rat CPIP model, Klafke et al. found that acute phase (day 1) CRPS was characterized by cell infiltration (increased tumor necrosis factor-$\alpha$, TNF-$\alpha$; myeloperoxidase, MPO; and $N$-acetyl-$\beta$-?-glucosaminidase, NAGase), cytokine and lactate production, increased levels of oxidative substances, and cold and mechanical allodynia.[47] The chronic phase (day 14) indicated increased oxidative stress and hypersensitivity to mechanical and cold stimuli. Furthermore, treatment with a transient receptor potential ankyrin 1 (TRPA1) channel antagonist (HC-030031) reduced mechanical and cold allodynia in the acute and chronic CRPS stages, but no change in TRPA1 immunoreactivity was observed. Reflecting that increased TRPA1 (a $Ca^{2+}$-permeable channel expressed in nociceptive neurons and also in astrocytes[51]) is not the cause of pain in this scenario, although considered to play a key role in neuropathic pain and neurogenic inflammation. Similar nociceptive findings were observed in the mouse CPIP model.[52] Another TRPA1 channel antagonist, CTK 01512–2, also reduced mechanical and cold allodynia after CPIP injury in both the acute and chronic CRPS phases. Additionally, treatment with bradykinin (BK) antagonists (HOE-140 and DALBK), mitigated the CPIP-induced mechanical allodynia and the oedematogenic response, suggesting the participation of BK receptors in the development and maintenance of chronic pain associated with the model.[53]

Immediate treatment of the CPIP mouse model after reperfusion with the 1-methylpropyl 2-imidazolyl disulfide (PX-12) drug, decreased the level of hypoxia inducible factor-1$\alpha$ (HIF-1$\alpha$) and pro-inflammatory cytokines (interleukin-1 beta; IL-1$\beta$).[49] The PX-12 drug reduced allodynia in a dose dependent manner for up to 24 hours, whereafter follow-up treatment did not demonstrate an analgesic effect. Although the PX-12 drug did not show long lasting analgesic effects, the HIF-1$\alpha$ inhibitor can be considered as a potential treatment target for the reduction of inflammatory cytokines and producing anti-allodynia analgesia.

Additionally, several clinical studies have investigated the role of the immune system and T-cells in the onset and maintenance of CRPS.[54–57] One study showed that plasma of CRPS patients had statistically significant elevated levels of sIL-2R as compared to healthy controls, indicating increased T-cell activity in CRPS patients.[54] Heyn et al. showed that CRPS patients, compared to healthy controls, has an altered T-cell system (Th17, Tregs and CD39) with decreased numbers of pro-inflammatory Th17 cells, an increased proportion of CD39$^+$ Tregs, and almost unchanged systemic cytokine levels.[54] Suggesting that the decrease in Th17 cells in CRPS is regulated by an increase in CD39$^+$ Tregs and that this anti-inflammatory T-cell shift may be a mechanism to control inflammation in CRPS.

A recent mass cytometry study has shown that chronic CRPS is associated with increased numbers of circulating central memory T lymphocytes (CD4$^+$ and CD8$^+$).[56] Particularly, type 1 helper T lymphocyte (Th1) and regulatory T lymphocyte (Treg) CD4+ subsets showed significant increases in number and increased NF$\kappa$B signaling. Decreased numbers of activated myeloid dendritic cells (CD1c$^+$) were observed in the peripheral circulation, indicative of tissue trafficking and involvement in T lymphocyte activation. These results may indicate ongoing inflammation and cellular damage in CRPS. In a follow-up study, the authors found that reduced IL-37 and tryptophan, and increased Tregs, CD8$^+$ T cells and granulocyte-macrophage colony-stimulating factor may be critical to the inflammatory activation seen in CRPS patients.[57]

## Neuroinflammatory mechanisms

To gain a further understanding of the acute and chronic CRPS phases, Cropper et al. used positron emission tomography (PET) to noninvasively track molecular processes in a mouse TFM.[58] They used a translocatorprotein-18 kDA (TSPO) PET tracer, $^{18}$FGE-180,[59] to monitor peripheral and central inflammatory responses over 20 weeks. Increased peripheral inflammation was observed 2 days after fracture and lasted for up to 7 weeks. Centralized inflammation was seen in the spinal cord and brain at 7 and 21 days after injury. Moreover, immunofluorescent staining of spinal cord tissue confirmed TSPO expression in microglia (CD11b1) at 7 days, whereas at baseline and week 7, TSPO was restricted to endothelial cells (PECAM11). This suggests that there is an early and persistent involvement of peripheral myeloid cells (e.g. macrophages) at the injury site, whereas transient central microglial activation was observed in the acute phase of CRPS. Microglial activation in the acute phase of CRPS is consistent with another animal study.[60]

Glia cells has been identified as one of the major causes of central sensitization and considered to play a role in the cause of chronic stage CRPS.[60–63] Acute

(3 weeks post-fracture) intrathecal treatment with interleukin-10 (IL-10), a potent anti-inflammatory cytokine, was administered in a mouse TFM to prevent the transition from acute to chronic stage CRPS.[64] IL-10 treatment only had an anti-allodynic effect in the acute stage of CRPS however, it did not prevent transition to the chronic stage.[64] It is thought that the anti-allodynic effects of IL-10 might be due to modulation of microglia activation, and the decrease in pro-inflammatory cytokines and neurokinin 1 (NK1) receptors in the spinal cord of the TFM. Additionally, a rat TFM, treated with LY303870 (NK1 receptor antagonist) 4 weeks after fracture, showed partial reversal of spinal glial activation and nociceptive sensitization.[60] However, treatments with minocycline (anti-inflammatory drug) and L-2-aminoadipicacid (LLA, astrocyte toxin/inhibitor), started 4 weeks post fracture, only partially reversed allodynia and unweighting in the fractured limb.

Furthermore, a pilot CRPS patient study, using [11C]-(R)-PK11195 PET and magnetic resonance spectroscopy (MRS) identified that central neuronal metabolites are also correlated with neuroinflammation.[44] Elevated neuroinflammation levels in CRPS seems to be primarily associated with lipids in the brain, which could be caused by microglia increase. High levels of glucose and pH correlated with increased neuroinflammation, whereas high levels of $CO_2$, basophil, and creatinine were associated with decreased neuroinflammation in the brains of CRPS patients. Moreover, interactions between central and peripheral metabolites in CRPS patients were distinct from those in healthy individuals, possibly supporting disrupted homeostasis between central and peripheral metabolites.[65] This could result from neuroinflammation and immune system dysfunction, emphasizing that a better understanding of peripheral biomarkers and metabolites are needed to understand CRPS pathophysiology.

## Autoimmunity

Apart from the neuroinflammatory mechanism, there is also a growing amount of evidence that supports autoimmunity in CRPS.[66] A mouse TFM showed that functional neuropeptide signaling (substance P and calcitonin gene-related peptide (CGRP)), contributed to development of post-fracture nociceptive sensitization and deposition of immunoglobulin M (IgM) autoantibodies in the skin, sciatic nerve and spinal cord. Moreover, increased numbers of Langerhans cells (LC) were observed in the skin of fracture mice and early (average duration 9.4 weeks) CRPS patients,[66] whereas decreased LCs were found in the skin of chronic (average duration 5.5 years) CRPS patients.[67] LC increases in mice were reduced in neuropeptide signaling-deficient animals and unexpectedly, nociceptive sensitization

after fracture in LC-deficient mice was normal. Suggesting that LCs are not required for the development of nociceptive changes after fracture despite their activation by neuropeptides.

In a follow up study, they found that IgM protein levels were elevated in the skin of fractured TFM mice (3 weeks post-fracture) and that their serum had pronociceptive effects when transferred to mice lacking B cells.[68] Pharmacological disruption of T follicular helper (Tfh)-B cell interactions in fracture mice, using Tfh signaling inhibitor (FK506), impaired germinal center reactions, reduced IgM accumulation in the injured limb, reduced nociceptive sensitization, and no pronociceptive serum effects could be transferred to fractured mice deficient of B cells. Consequently, demonstrating that TFM induces an adaptive autoimmune response characterized by popliteal lymph node germinal center formation and Tfh cell dependent B cell activation that results in nociceptive sensitization within 3 weeks.

Furthermore, in a translational passive transfer trauma mouse model of CRPS, Helyes et al. found that persistent CRPS is contributed to by autoantibodies.[69] Animals receiving daily injections of purified serum immunoglobulin G (IgG) from patients with longstanding CRPS developed significantly increased and prolonged swelling, and stable hyperalgesia of the incised paw compared to IgG from healthy controls. CRPS IgG-injected mice also presented with sustained, extreme microglia and astrocyte activation in the dorsal horn of the spinal cord and pain-related brain regions, suggesting central sensitization.

## Genetic effects

Recently, two studies investigated differentially regulated genes (DEGs) in a CPIP rat model to determine which genes are relevant to pain and neuroinflammation mechanisms in CRPS.[70,71] Compared to the sham group (same CPIP procedure without perfusion block), DEG profiles in the ipsilateral dorsal root ganglion (DRG)[70] and ipsilateral spinal cord dorsal horn (SCDH)[71] showed significant gene changes, some well-established in the inflammation and pain processes. In the ipsilateral SCDH, rats also showed significant activation of microglia and astrocytes.[71]

Furthermore, a gene ontology (GO) analysis showed that upregulated genes in DRGs in the CPIP vs sham groups, were mostly involved in response to lipopolysaccharide, inflammation, G-protein coupled receptor binding, cytokine activity, and neuropeptide signaling.[70] Whereas upregulated genes in the SCDH of CPIP vs sham group were related with inflammation and innate immune response, defense response to virus, positive regulation of T-cell proliferation and Toll-like receptor signaling pathway.[71] Additionally, the GO analysis showed

that the ERK1/2 cascade, suggested to play a crucial role in mediating pain,[72–74] was also among the significantly enriched pathways of upregulated genes in the DRGs.[70] These results suggest that neuroinflammation in both the DRG and SCDH could be a predominant process in CRPS pathophysiology.[70,71]

In another study, Nahm et al. investigated the involvement of the central nervous system in the development and maintenance of CRPS.[75] Cerebral expression of NFκB was found to be increased in the CPIP animal model, implementing that a minor peripheral injury can affect the brain which may also have implications for CRPS.[75] Although the role of NFκB in CRPS pathogenesis is unclear, its increased expression in the cerebrum might play a role in the pathogenesis of pain in the CPIP model and human CRPS.

Additionally, DEGs identified in the blood samples from 4 CRPS patients revealed that HLA-DQB1, HLA-DRB4, and HLA-DRB1 genes from the human leukocyte antigen (HLA) family were most significantly differentially expressed.[76] These genes may present potential biomarkers for the diagnosis of CRPS. Furthermore, protein-protein interaction network analysis revealed that key genes, namely region 1 A binding protein p300, CREB-binding protein, signal transducer and activator of transcription (STAT)3, and STAT5A may be important in the development of CRPS. This study also provides additional evidence supporting the hypothesis that neuro-autoimmunity plays an important role in CRPS pathogenesis.

### Neuromodulation and inflammation

Kriek et al. recently investigated whether SCS treatment had immunomodulatory properties. Blister fluid of CRPS patients after SCS showed a decreased expression of both anti- and pro-inflammatory cytokines over time in the CRPS affected limb as well as the contralateral limb. The chemokine levels of IP-10 and Eotaxin, and the growth factors VEGF and PDGFBB were also reduced bilaterally over time. This diminished effect could possibly be due to improved peripheral tissue oxygenation after the reduction of anti-angiogenetic activity of IP-10, resulting in diminished endothelial dysfunction and improved flood flow. Furthermore, before and after SCS, there were no significant changes in IL-6 and TNF-α in the affected extremity compared to the contralateral extremity. Overall, improved sudomotor, vasomotor, and sensory signs/symptoms were observed after SCS.[77] This corresponded to the findings of a previous CRPS patient study which also examined blister fluid of CRPS patients and found bilaterally increased proinflammatory TNF-a and MIP-1b and decreased anti-inflammatory IL-1RA protein levels compared to non-CRPS patients. After undergoing 6 months of analgesic

treatment, the protein levels of all measured cytokines in CRPS patients, except for IL-6, significantly changed bilaterally to the level of non-CRPS patients.[78]

Similar to SCS, limited information is available on the immunomodulatory properties of targeted DRGS which has also been shown to suppress pain and improve the functional capacity in CRPS patients.[16] A recent preliminary clinical trial detected increased peripheral concentrations of pro-inflammatory molecular mediators in CRPS patients.[16] After 3 months of unilateral L4-DRGs, serum anti-inflammatory IL-10 significantly decreased while saliva oxytocin concentrations increased in CRPS subjects, with significant improvement noted in neuropathic pain and functional impairment.[16] In a follow-up study, using blood samples from L4-DRGS treated CRPS patients, the authors aimed to determine the gene expression changes in the whole transcriptome.[20] The gene expression profile revealed several significantly up- and down-regulated genes that were involved in immune-inflammatory circuits that could indicate a possible relation to the pathophysiology of CRPS. However, further research is needed to determine how L-4 DRGS influences the pathophysiology of CRPS. Larger biobank approaches are necessary to establish a genetic phenotype for CRPS patients.

## Discussion

In this narrative review we assessed the main findings of 16 preclinical and 8 clinical studies that highlighted current developments in CRPS pathophysiological research. As previously confirmed, CRPS is a heterogenous pain syndrome with various clinical presentations that change over time.[34] Typically, the acute and chronic phases of CRPS are characterized by the activation of different inflammatory mechanisms and cellular processes, however the exact role and progression of these processes are not fully understood.[58] These characteristics make CRPS particularly difficult to treat and therefore current research is still driven to gain a better understanding of the pathophysiology of the disease.[34] Most studies reviewed here, seems to provide increasing evidence and support for a role of inflammation and neuroinflammation in CRPS pathophysiology.

A CPIP model study, identified that the acute phase showed mainly inflammatory and oxidative stress-related detectable parameters, whereas the chronic phase revealed increased levels of oxidative by-products which could contribute to continuous nociceptive activation.[50] Furthermore, TRPA1, BK receptors and HIF-1α has been identified as alternative treatment targets for the management of CRPS pain and inflammation.[49,50,53] Several clinical studies have also highlighted that the immune system and T-cells are critical components in the pathophysiology of CRPS

patients.[54–57] This is consistent with the findings in a neuropathic animal model and CRPS patients.[79,80]

Central inflammation was found to be present in the spinal cord and brain of a TFM and consistent with another animal study, microglial activation was observed in the acute phase of TFM-induced CRPS.[58,60] Although glia cells has been implicated as a causes of chronic stage CRPS,[56–59] treatment attempts of animal models with glial receptor antagonists (IL-10, LY303870) only reduced anti-allodynic effects in the acute stage but failed to prevent disease progression to the chronic stage.[60,64]

As a marker of glial activation, elevated myo-inositol or MI has been associated with neuropathic pain[81,82] and CRPS.[83] In the H-MRS CRPS patient study by Jung et al., MI was however not obviously related to the increase in neuroinflammation.[44] Instead, they found positive correlations of Lipid (Lip)13a/total creatine (tCr) and Lip09/tCr with neuroinflammation in CRPS patients, which were not found in controls. High lipid levels may be a biomarker for underlying neuroinflammation in CRPS.[44]

Autoimmunity might also play a role in the development of CRPS.[13] This has been demonstrated in a mouse TFM, which induced an adaptive autoimmune response characterized by popliteal lymph node germinal center formation and Tfh cell dependent B cell activation.[68] Furthermore, neuropeptide signaling in the fractured limb of mice also seems to mediate autoantigenic IgM production and nociceptive sensitization.[66] Autoreactive IgM might be a useful biomarker for CRPS cases with a strong immune contribution, whereas anti-substance P and anti-CGRP signaling strategies could reduce post-traumatic autoimmunity.

Based on the reviewed pathological mechanisms described here, and the role of neuroinflammation in CRPS, there seems to be a strong rationale for considering neurostimulation approaches to treat CRPS pain. Particularly since there is a growing understanding that all forms of pain are ultimately the result of interactions between central and peripheral properties of the nervous system, which in turn allows neurostimulation therapies to interact with inflammatory pain signaling.[20] SCS and DRGS treatment have shown great success in the treatment of neuropathic-like pain in CRPS patients, however both preclinical and clinical literature on its potential immunomodulatory effects are scarce. Further research is needed to unravel the immunomodulatory mechanisms of action of SCS and DRGS, which could in future allow for personalized neurostimulation therapy.

## Author Contributions

All authors contributed to the planning, conduct, reporting, conception and design, analysis and interpretation of data in this manuscript.

## ORCID iD

Amrita Prasad (iD) https://orcid.org/0000-0003-2595-1286

## References

1. de Mos M, de Bruijn A, Huygen F, Dieleman J, Stricker B, Sturkenboom M. The incidence of complex regional pain syndrome: a population-based study. *Pain* 2007; 129: 12–20.
2. Sandroni P, Benrud-Larson L, McClelland R, Low P. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain* 2003; 103: 199–207.
3. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet* 1993; 342: 1012–1016.
4. Shim H, Rose J, Halle S, Shekane P. Complex regional pain syndrome: a narrative review for the practising clinician. *Br J Anaesth* 2019; 123: e424–e433. e
5. Harden R, Bruehl S, Roberto P, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Chont M, Vatine J. Validation of proposed diagnostic criteria (the "budapest criteria") for complex regional pain syndrome. *Pain* 2010; 150: 268–274.
6. de Mos M, Huygen F, Hoeven-Borgman M, Dieleman J, Stricker B, Sturkenboom M. Outcome of the complex regional pain syndrome. *Clin J Pain* 2009; 25: 590–597.
7. Ott S, Maihofner C. Signs and symptoms in 1,043 patients with complex regional pain syndrome. *J Pain* 2018; 19: 599–597.
8. Kim H, Lee CH, Kim SH, Kim YD. Epidemiology of complex regional pain syndrome in Korea: an electronic population health data study. *PLoS One* 2018; 13: e0198147.
9. Bruehl S. An update on the pathophysiology of complex regional pain syndrome. *Anesthesiology* 2010; 113: 713–725.
10. Kortekaas M, Niehof S, Stolker R, Huygen F. Pathophysiological mechanisms involved in vasomotor disturbances in complex regional pain syndrome and implications for therapy: a review. *Pain Pract* 2016; 16: 905–914.
11. O'Connell N, Wand B, McAuley J, Marston L, Moseley L. Interventions for treating pain and disability in adults with complex regional pain syndrome. *Cochrane Database Syst Rev* 2013; 4: CD009416.

12. Bruehl S. Complex regional pain syndrome. *BMJ (Online)* 2015; 351: h2710.

13. Eldufani J, Elahmer N, Blaise G. A medical mystery of complex regional pain syndrome. *Heliyon* 2020; 6: e03329.

14. Fishman M, Antony A, Esposito M, Deer T, Levy R. The evolution of neuromodulation in the treatment of chronic pain: forward-looking perspectives. *Pain Med* 2019; 20: S58–S68.

15. Chaudhry SR, Lendvai IS, Muhammad S, Westhofen P, Kruppenbacher J, Scheef L, Boecker H, Scheele D, Hurlemann R, Kinfe TM. Inter-ictal assay of peripheral circulating inflammatory mediators in migraine patients under adjunctive cervical non-invasive vagus nerve stimulation (nVNS): a proof-of-concept study. *Brain Stimul* 2019; 12: 643–651.

16. Gravius N, Chaudhry S, Muhammad S, Bostrom A, Gravius S, Randau T, Scheele D, Westhofen P, Kruppenbacher J, Stoffel-Wagner B, Maier C, Weidlich A, Yearwood T, Chakravarthy K, Kramer J, Hurlemann R, Kinfe T. Selective L4 dorsal root ganglion stimulation evokes pain relief and changes of inflammatory markers: Part I profiling of saliva and serum molecular patterns. *Neuromodulation* 2019; 22: 44–52.

17. Muhammad S, Chaudhry S, Yearwood T, Krauss J, Kinfe T. Changes of metabolic disorders associated peripheral cytokine/adipokine traffic in non-obese chronic back patients responsive to burst spinal cord stimulation. *Neuromodulation* 2018; 21: 31–37.

18. Kinfe T, Muhammad S, Link C, Roeske S, Chaudhry S, Yearwood T. Burst spinal cord stimulation increases peripheral antineuroinflammatory interleukin 10 levels in failed back surgery syndrome patients with predominant back pain. *Neuromodulation* 2017; 20: 322–330.

19. Jensen M, Hakimian S, Sherlin L, Fregni F. New insights into neuromodulatory approaches for the treatment of pain. *J Pain* 2008; 9: 193–199.

20. Kinfe T, Asif M, Chakravarthy K, Deer T, Kramer J, Yearwood T, Hurlemann R, Hussain M, Motameny S, Wagle P, Nürnberg P, Gravius S, Randau T, Gravius N, Chaudhry S, Muhammad S. Unilateral L4-dorsal root ganglion stimulation evokes pain relief in chronic neuropathic postsurgical knee pain and changes of inflammatory markers: Part II whole transcriptome profiling. *J Transl Med* 2019; 17: 205.

21. Dirckx M, Stronks D, Groeneweg G, Huygen F. Effect of immunomodulating medications in complex regional pain syndrome: systematic review. *Clin J Pain* 2012; 28: 355–363.

22. Deer T, Grider J, Lamer T, Pope J, Falowski S, Hunter C, Provenzano D, Slavin K, Russo M, Carayannopoulos A, Shah J, Harned M, Hagedorn J, Bolash R, Arle J, Kapural L, Amirdelfan K, Jain S, Liem L, Carlson J, Malinowski M, Bendel M, Yang A, Aiyer R, Valimahomed A, Antony A, Craig J, Fishman M, Al-Kaisy A, Christelis N, Rosenquist R, Levy R, Mekhail N. A systematic literature review of spine neurostimulation therapies for the treatment of pain. *Pain Med* 2020; 21: 1421–1432.

23. Deer T, Hunter C, Mehta P, Sayed D, Grider J, Lamer T, Pope J, Falowski S, Provenzano D, Esposito M, Slavin K, Baranidharan G, Russo M, Jassal N, Mogilner A, Kapural L, Verrills P, Amirdelfan K, McRoberts W, Harned M, Chapman K, Liem L, Carlson J, Yang A, Aiyer R, Antony A, Fishman M, Al-Kaisy A, Christelis N, Levy R, Mekhail N. A systematic literature review of dorsal root ganglion neurostimulation for the treatment of pain. *Pain Med* 2020; 21: 1581–1589.

24. Harrison C, Epton S, Bojanic S, Green A, FitzGerald J. The efficacy and safety of dorsal root ganglion stimulation as a treatment for neuropathic pain: a literature review. *Neuromodulation* 2018; 21: 225–233.

25. Deer T, Levy R, Kramer J, Poree L, Amirdelfan K, Grigsby E, Staats P, Burton A, Burgher A, Obray J, Scowcroft J, Golovac S, Kapural L, Paicius R, Kim C, Pope J, Yearwood T, Samuel S, McRoberts W, Cassim H, Netherton M, Miller N, Schaufele M, Tavel E, Davis T, Davis K, Johnson L, Mekhail N. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *Pain* 2017; 158: 669–681.

26. Liem L, Russo M, Huygen F, Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. *Neuromodulation* 2015; 18: 41–48; discussion 48–49.

27. Liem L, Russo M, Huygen F, Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. *Neuromodulation* 2013; 16: 471–482; discussion 482.

28. Liem L, Dongen E, Huygen F, Staats P, Kramer J. The dorsal root ganglion as a therapeutic target for chronic pain. *Reg Anesth Pain Med* 2016; 41: 511–519.

29. Willis W. Dorsal root potentials and dorsal root reflexes: a double-edged sword. *Exp Brain Res* 1999; 124: 395–421.

30. Wang J, Ren Y, Zou X, Fang L, Willis W, Lin Q. Sympathetic influence on capsaicin-evoked enhancement of dorsal root reflexes in rats. *J Neurophysiol* 2004; 92: 2017–2026.

31. Vuka I, Vucic K, Repic T, Hamzic L, Sapunar D, Puljak L. Electrical stimulation of dorsal root ganglion in the context of pain: a systematic review of in vitro and in vivo animal model studies. *Neuromodulation* 2018; 21: 213–224.

32. Kent A, Min X, Hogan Q, Kramer J. Mechanisms of dorsal root ganglion stimulation in pain suppression: a computational modeling analysis. *Neuromodulation* 2018; 21: 234–246.

33. Liberati A, Altman D, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidi J, Clarke M, Devereaux P, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *BMJ* 2009; 339: b2700.

34. Birklein F, Ajit S, Goebel A, Perez R, Sommer C. Complex regional pain syndrome—phenotypic characteristics and potential biomarkers. *Nat Rev Neurol* 2018; 14: 272–284.

35. Bruehl S, Maihofner C, Stanton-Hicks M, Perez R, Vatine JJ, Brunner F, Birklein F, Schlereth T, Mackey S, Mailis-Gagnon A, Livshitz A, Harden R. Complex regional pain syndrome: evidence for warm and cold subtypes in a large prospective clinical sample. *Pain* 2016; 157: 1674–1681.

36. Bharwani K, Dik W, Dirckx M, Huygen F. Highlighting the role of biomarkers of inflammation in the diagnosis and management of complex regional pain syndrome. *Mol Diagn Ther* 2019; 23: 615–626.

37. Borchers A, Gershwin M. Complex regional pain syndrome: a comprehensive and critical review. *Autoimmun Rev* 2014; 13: 242–265.

38. Hall J, Brain S. Pharmacology of calcitonin gene-related peptide. In: Geppetti P, Holzer P (eds) *Neurogenic inflammation*. Boca Raton: CRC Press LLC, 1996.

39. Holzer P. Neurogenic vasodilatation and plasma leakage in the skin. *Gen Pharmacol* 1998; 30: 5–11.

40. Weber M, Birklein F, Neundorfer B, Schmelz M. Facilitated neurogenic inflammation in complex regional pain syndrome. *Pain* 2001; 91: 251–257.

41. Birklein F, O'Neill D, Schlereth T. Complex regional pain syndrome: an optimistic perspective. *Neurology* 2015; 84: 89–96.

42. van Velzen G, Rombouts S, van Buchem M, Marinus J, van Hilten J. Is the brain of complex regional pain syndrome patients truly different? *Eur J Pain* 2016; 20: 1622–1633.

43. König S, Schlereth T, Birklein F. Molecular signature of complex regional pain syndrome (CRPS) and its analysis. *Expert Rev Proteom* 2017; 14: 857–867.

44. Jung Y, Kim H, Jeon S, Kwon J, Lee W, Kim Y, Jang J, Choi S, Lee J, Kang D. Brain metabolites and peripheral biomarkers associated with neuroinflammation in complex regional pain syndrome using [11C]-(R)-PK11195 positron emission tomography and magnetic resonance spectroscopy: a pilot study. *Pain Med* 2019; 20: 504–514.

45. Jeon S, Seo S, Lee J, Choi S, Lee DH, Jung Y, Song M, Lee K, Kim Y, Kwon H, Im H, Lee DS, Cheon G, Kang D. [11C]-(R)-PK11195 positron emission tomography in patients with complex regional pain syndrome: a pilot study. *Medicine (Baltimore)* 2017; 96: e5735.

46. Ji R, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and Central sensitization in chronic and widespread pain. *Anesthesiology* 2018; 129: 343–366.

47. Xanthos D, Sandkuhler J. Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. *Nat Rev Neurosci* 2014; 15: 43–53.

48. Birklein F, Ibrahim A, Schlereth T, Kingery W. The rodent tibia fracture model: a critical review and comparison with the complex regional pain syndrome literature. *J Pain* 2018; 19: 1102.e1–1102.e19.

49. Hsiao H, Hsiao H, Lin Y, Wang J, Tsai Y, Liu Y. Hypoxia inducible factor-1α inhibition produced anti-allodynia effect and suppressed inflammatory cytokine production in early stage of mouse complex regional pain syndrome model. *Clin Exp Pharmacol Physiol* 2016; 43: 355–359.

50. Klafke J, da Silva M, Rossato M, De Prá S, Rigo F, Walker C, Bochi G, Moresco R, Ferreira J, Trevisan G. Acute and chronic nociceptive phases observed in a rat hind paw ischemia/reperfusion model depend on different mechanisms. *Pflugers Arch* 2016; 468: 229–241.

51. Vellani V, Gomis-Perez C, Pinti M, Prandini M, Pavesi G, Giacomoni C, Caprini M. TRPA1 is expressed in Central but not in peripheral glia. *JBiSE* 2016; 09: 515–531.

52. De Prá S, Antoniazzi C, Ferro P, Kudsi S, Camponogara C, Fialho M, Rigo F, Gomez M, Bochi G, Moresco R, Oliveira S, Trevisan G. Nociceptive mechanisms involved in the acute and chronic phases of a complex regional pain syndrome type 1 model in mice. *Eur J Pharmacol* 2019; 859: 172555.

53. Gonçalves E, Vieira G, Gonçalves T, Simões R, Brusco I, Oliveira S, Calixto J, Cola M, Santos A, Dutra R. Bradykinin receptors play a critical role in the chronic post-ischaemia pain model. *Cell Mol Neurobiol* 2021; 41: 63–78.

54. Bharwani K, Dirckx M, Stronks D, Dik W, Schreurs M, Huygen F. Elevated plasma levels of sIL-2R in complex regional pain syndrome: a pathogenic role for T-Lymphocytes? *Mediators Inflamm* 2017; 2017: 1–6.

55. Heyn J, Azad S, Luchting B. Altered regulation of the T-cell system in patients with CRPS. *Inflamm Res* 2019; 68: 1–6.

56. Russo M, Fiore N, Vreden C, Bailey D, Santarelli D, McGuire H, St Groth B, Austin P. Expansion and activation of distinct central memory T lymphocyte subsets in complex regional pain syndrome. *J Neuroinflammation* 2019; 16: 1–17.

57. Russo M, Georgius P, Pires A, Heng B, Allwright M, Guennewig B, Santarelli D, Bailey D, Fiore N, Tan V, Latini A, Guillemin G, Austin P. Novel immune biomarkers in complex regional pain syndrome. *J Neuroimmunol* 2020; 347: 577330.

58. Cropper H, Johnson E, Haight E, Cordonnier S, Chaney A, Forman T, Biswal A, Stevens M, James M, Tawfik V. Longitudinal translocator protein-18 kDa-positron emission tomography imaging of peripheral and Central myeloid cells in a mouse model of complex regional pain syndrome. *Pain* 2019; 160: 2136–2148.

59. Wadsworth H, Jones PA, Chau W-F, Durrant C, Fouladi N, Passmore J, O'Shea D, Wynn D, Morisson-Iveson V, Ewan A, Thaning M, Mantzilas D, Gausemel I, Khan I, Black A, Avory M, Trigg W. [(1)(8)F]GE-180: a novel fluorine-18 labelled PET tracer for imaging translocator protein 18 kDa (TSPO.). *Bioorg Med Chem Lett* 2012; 22: 1308–1313.

60. Li W, Guo TZ, Shi X, Sun Y, Wei T, Clark D, Kingery W. Substance P spinal signaling induces glial activation and nociceptive sensitization after fracture. *Neuroscience* 2015; 310: 73–90.

61. Linnman C, Becerra L, Borsook D. Inflaming the brain: CRPS a model disease to understand neuroimmune interactions in chronic pain. *J Neuroimmune Pharmacol* 2013; 8: 547–563.

62. Banati R. Neuropathological imaging: in vivo detection of glial activation as a measure of disease and adaptive change in the brain. *Br Med Bull* 2003; 65: 121–131.

63. Banati R, Cagnin A, Brooks D, Gunn R, Myers R, Jones T, Birch R, Anand P. Long-term trans-synaptic glial

responses in the human thalamus after peripheral nerve injury. *Neuroreport* 2001; 12: 3439–3442.

64. Kim J, Park J, Park D. Anti-allodynic effect of interleukin 10 in a mouse model of complex regional pain syndrome through reduction of NK1 receptor expression of microglia in the spinal cord. *J Pain Res* 2018; 11: 1729–1741.

65. Jung Y, Kim H, Lee D, Lee J, Lee W, Moon J, Kim Y, Choi S, Kang D. Disruption of homeostasis based on the right and left hemisphere in patients with complex regional pain syndrome. *NeuroImmunoModulation* 2019; 26: 276–284.

66. Li W, Guo T, Shi X, Birklein F, Schlereth T, Kingery W, Clark D. Neuropeptide regulation of adaptive immunity in the tibia fracture model of complex regional pain syndrome. *J Neuroinflammation* 2018; 15: 105.

67. Osborne S, Farrell J, Dearman RJ, MacIver K, Naisbitt DJ, Moots RJ, Edwards SW, Goebel A. Cutaneous immunopathology of long-standing complex regional pain syndrome. *Eur J Pain* 2015; 19: 1516–1526.

68. Li W, Yang Y, Shi X, Guo T, Guang Q, Kingery W, Herzenberg L, Clark J. Germinal center formation, immunoglobulin production and hindlimb nociceptive sensitization after tibia fracture. *Brain Behav Immun* 2020; 88: 725–734.

69. Helyes Z, Tékus V, Szentes N, Pohóczky K, Botz B, Kiss T, Kemény A, Környei Z, Tóth K, Lénárt N, Ábrahám H, Pinteaux E, Francis S, Sensi S, Dénes A, Goebel A. Transfer of complex regional pain syndrome to mice via human autoantibodies is mediated by interleukin-1–induced mechanisms. *Proc Natl Acad Sci U S A* 2019; 116: 13067–13076.

70. Yin C, Hu O, Liu B, Tai Y, Zheng X, Li Y, Xiang X, Wang P, Liu B. Transcriptome profiling of dorsal root ganglia in a rat model of complex regional pain syndrome type-I reveals potential mechanisms involved in pain. *J Pain Res* 2019; 12: 1201–1216.

71. Chen R, Yin C, Hu O, Liu B, Tai Y, Zheng X, Li Y, Fang J, Liu B. Expression profiling of spinal cord dorsal horn in a rat model of complex regional pain syndrome type-I uncovers potential mechanisms mediating pain and neuroinflammation responses. *J Neuroinflammation* 2020; 17: 1–19.

72. Borges G, Berrocoso E, Mico J, Neto F. ERK1/2: Function, signaling and implication in pain and pain-related anxio-depressive disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2015; 60: 77–92.

73. Cruz CD, Neto FL, Castro-Lopes J, McMahon SB, Cruz F. Inhibition of ERK phosphorylation decreases

nociceptive behaviour in monoarthritic rats. *Pain* 2005; 116: 411–419.

74. Xing F, Kong C, Bai L, Qian J, Yuan J, Li Z, Zhang W, Xu J-T. CXCL12/CXCR4 signaling mediated ERK1/2 activation in spinal cord contributes to the pathogenesis of postsurgical pain in rats. *Mol Pain* 2017; 13: 1744806917718753.

75. Nahm F, Nahm S, Han W, Gil H, Choi E, Lee P. Increased cerebral nuclear factor kappa B in a complex regional pain syndrome rat model: possible relationship between peripheral injury and the brain. *J Pain Res* 2019; 12: 909–914.

76. Tan W, Song Y, Mo C, Jiang S, Wang Z. Analysis of gene expression profile microarray data in complex regional pain syndrome. *Mol Med Rep* 2017; 16: 3371–3378.

77. Kriek N, Schreurs M, Groeneweg G, Dik W, Tjiang G, Gültuna I, Stronks D, Huygen F. Spinal cord stimulation in patients with complex regional pain syndrome: a possible target for immunomodulation? *Neuromodulation* 2018; 21: 77–86.

78. Lenz M, Üçeyler N, Frettlöh J, Höffken O, Krumova E, Lissek S, Reinersmann A, Sommer C, Stude P, Waaga-Gasser A, Tegenthoff M, Maier C. Local cytokine changes in complex regional pain syndrome type I (CRPS I) resolve after 6 months. *Pain* 2013; 154: 2142–2149.

79. Hu P, Bembrick A, Keay K, McLachlan E. Immune cell involvement in dorsal root ganglia and spinal cord after chronic constriction or transection of the rat sciatic nerve. *Brain Behav Immun* 2007; 21: 599–616.

80. Kaufmann I, Eisner C, Richter P, Huge V, Beyer A, Chouker A, Schelling G, Thiel M. Lymphocyte subsets and the role of TH1/TH2 balance in stressed chronic pain patients. *Neuroimmunomodulation* 2007; 14: 272–280.

81. Chang L, Munsaka S, Kraft-Terry S, Ernst T. Magnetic resonance spectroscopy to assess neuroinflammation and neuropathic pain. *J Neuroimmune Pharmacol* 2013; 8: 576–593.

82. Pattany PM, Yezierski RP, Widerström-Noga EG, Bowen BC, Martinez-Arizala A, Garcia BR, Quencer RM. Proton magnetic resonance spectroscopy of the thalamus in patients with chronic neuropathic pain after spinal cord injury. *Am J Neuroradiol* 2002; 23: 901–905.

83. Grachev I, Thomas P, Ramachandran T. Decreased levels of N-acetylaspartate in dorsolateral prefrontal cortex in a case of intractable severe sympathetically mediated chronic pain (complex regional pain syndrome, type I). *Brain Cogn* 2002; 49: 102–113.