

Review

An embarrassment of pain perceptions? Towards an understanding of and explanation for the clinical presentation of CRPS type 1

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Complex regional pain syndrome (CRPS), a fairly common problem in rheumatological and orthopaedic practice, is an allodynic pain state of uncertain pathology often variably and unpredictably responsive to treatments. Although published diagnostic criteria are available, in the reality of clinical practice these do not appear to encompass the wide variety of symptoms that a patient may present with. This leads to scepticism on the part of the clinician and confusion for the sufferer. This article aims to provide some explanations for an often bewildering clinical picture. We provide a construct for the plethora of symptoms that we have entitled 'the embarrassment of pain perceptions'. With the aid of a case report we examine recent research that suggests how peripherally based symptoms and signs arise from changes within the central nervous system, with particular attention given to the control function of the motor–proprioceptive integrative system. We speculate how these changes within the central nervous system may provide the patient with CRPS the ability to access complex layers of lower level perceptions that are normally suppressed. We propose that such a system may explain some of the clinical puzzlements seen in this condition and suggest that the complexities of CRPS may provide an insight into brain development through evolution, which is a fruitful area for interdisciplinary clinical and scientific research.

KEY WORDS: Complex regional pain syndrome, Pain, Motor control system.

Introduction

It is well known that the relationship between the degree of injury and the level of pain experienced is poor. It has been realized, but recently, that the reasons for this are indeed multifarious. However, descriptions of excessive pain in the presence of minor, or no injury accompanied by a disgust and neglect of an apparently functional limb are still commonly considered indicative of a somatoform disorder that may be cared for by our colleagues in psychiatry rather than the classical presentation of complex regional pain syndrome (CRPS). We suggest that our failure to appreciate that pains are simply one manifestation of multiple responses to injury, or the perceived threat of injury, lies at the heart of our difficulties. This provides a fundamental reason for our limited ability to progress treatments in chronic allodynic pain states, particularly those unresponsive, or only partially responsive, to the most powerful of analgesics, opiates. We are, we suggest, approaching the problem in the wrong way. This article will discuss recent research, supported by a case report that suggests that the seemingly bizarre clinical descriptions by a patient with CRPS may arise from changes in the central nervous system. Furthermore, we will propose that these changes enable access to lower brain perceptions that contribute additionally to the patient's symptomatology. It is not our intention to cover theories on peripheral mechanisms or assess the evidence for therapeutic options and management techniques as these have been extensively covered elsewhere [1–7].

CRPS may arise following major nerve damage (type II), minor trauma or spontaneously (type I). The onset of symptoms may be immediate but for the majority it is within 1 month of trauma or on immobilization of a limb, such as casting after a fracture [8]. Approximately, 50% of the sufferers go on to develop chronic

symptoms and long-term physical impairment [9, 10]. Disturbances in sensory, motor and autonomic pathways are present usually in a single limb, though it may occur in multiple limbs and other body regions [11–13]. The degree of disturbance in any one of these systems may be variable across time and even fluctuate on an hourly basis. Published incidence rates of CRPS range from 5.46 to 26.2 per 100 000 person-years with the wide range indicative of the problems with diagnosis and the multiple professions that sufferers often encounter before a diagnosis is confirmed [14, 15]. This is further complicated by the many names by which CRPS has been known in the past [11] and the close similarity in nomenclature between 'complex' and 'chronic' regional pain syndrome.

Clinical presentation

CRPS was eloquently first described by Weir Mitchell in 1872 [16] having witnessed the experience of injured soldiers in the American Civil War. The suffering of one particular soldier with causalgia (CRPS type II) is described in some detail.

On the second day the pain began. It was burning and darting. . . sensation was lost or lessened in the limb, and . . . paralysis of motion came on in the hand and forearm. The pain was so severe that a touch anywhere, or shaking of the bed, or a heavy step, caused it to increase.

Two years later the pain was still at the level where the soldier could not tolerate 'Friction of the clothes, at any point of the entire surface . . .' as this 'shoots into the hand' increasing his burning pain. He would allow no one to touch him 'except with a wetted hand, and even then is careful to exact careful manipulation'.

These descriptions capture the intensely distressing nature of CRPS and the disparate range of seemingly bizarre symptoms that a patient may describe. We present here a case report of a female patient with CRPS type I who was treated at the Royal National Hospital for Rheumatic Diseases in Bath, UK some 130 yrs after Weir Mitchell's soldier, but whose symptoms and descriptions bear a striking similarity to those he wrote of.

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A case of CRPS: an embarrassment of perceptions

Case report

A woman aged 42 yrs presented at the CRPS clinic with CRPS type 1 in the left hand 7 months after suffering a severe viral (herpes labialis) infection of her mouth. The infection had resulted in intense pain in her mouth and throat, and widespread musculoskeletal pains. Approximately 2 months after successful treatment and resolution of her viral symptoms she reported a spontaneous onset of pain in her left hand. This initially focused around her left index finger and wrist but the pain gradually extended up her arm to her elbow. At the time she had significant swelling of the lower arm, loss of hair over the painful site and an increase in nail growth on the left hand only. She reported that the limb had felt intensely hot compared with her right, and fluctuated between a dusky purple colour and a more mottled version of her right arm. As she was a busy farmer's wife she had continued to be involved in the daily activities of the farm, including milking the cows, and had been surprised to find that use of her left arm, although painful at the time, had actually helped to improve the pain somewhat.

Five months after her symptom onset she presented at the clinic and positioned herself in the clinic chair so that her left arm was protected from casual passers-by and she did not use her left arm in her normal gestures as she recounted her story (see Table 1 for a summary of signs and symptoms). She described her pain as 'burning' in quality and exacerbated by movement, cold water and vibration (particularly travelling in the car). When her pain was severe she was aware of a 're-awakening' of the pain in her mouth and on the left side of her face, similar to the one that she had experienced with her viral infection. She was also aware that stress exacerbated all her symptoms and found it perplexing that they could vary so much over the time course of the day, particularly the colour and temperature changes. Although trying to remain as active as possible she chose to avoid social situations as she found noisy environments intolerable and was fearful of others 'knocking into' her limb. Only on careful questioning did she reveal that although hypervigilant of her painful limb, as her positioning and manner clearly indicated, she felt that the limb did not 'belong

to her' from her elbow downwards. She also had a strong desire to amputate her left limb and could illustrate with her right hand the exact point at which she felt the incision should be placed. Above this site, her arm was perceived by her as 'normal' and 'belonging to her'.

On examination, there was clear evidence of autonomic changes with unilateral colour and temperature changes. The left lower arm felt warmer to touch than the right, and the left upper arm cooler. An objective temperature difference of $>2.5^{\circ}\text{C}$ between the right and left hands was confirmed via infrared thermal imaging (Fig. 1). The left hand and wrist were oedematous and the nails longer than on the right. There was a full range of movement at the left elbow and shoulder but it was reduced in the wrist. The patient was able to oppose all fingers to the thumb but the movement was painful and slow on the affected side. No attempt to passively manipulate the limb was made due to the patient's intense fear of touch. Allodynia to light touch and hyperalgesia to pin prick extended from finger tips to just above the left elbow. Standardized quantitative sensory testing using von Frey hairs demonstrated a raised mechanical detection threshold on the left arm (left 2.44 g, right arm 2.83 g) but no other hemisensory discrepancies on the trunk or lower limbs.

When approached by the examiner, level with her left arm, the patient reported that she was aware of a tingling sensation in her left hand and an increase in the pain. This response to the threat of touch, a non-painful stimulus evoking a painful response, we have termed 'conflict' allodynia as we perceive the response is generated by the threat of an encounter with the examiner. These painful perceptions were reported by the patient when the examiner's hand was ~ 30 cm from them and it was heightened in intensity the closer the examiner moved his/her hand towards the left wrist despite giving firm reassurance that the limb would never actually be touched. When the same procedure was repeated, but the examiner was level with the left side of the patient's face, she again reported the changes in sensation in her left hand.

When asked to close her eyes and 'visualize' the left limb she reported that she perceived her left hand as significantly larger than the right and her left arm shorter than the right between the elbow and wrist. She had not been aware of these altered body perceptions prior to undertaking this assessment and they were lost when she actively looked at her left limb. There was evidence of widespread referred sensations [17] with touch to the left side of her face and axilla referred to the underside of her left wrist, and touch to the right wrist identically matched to the left. The patient struggled to identify the individual digits on her left hand when asked to number them as they were touched, but had no problems with those on her right.

With a trial of mirror visual feedback [18] she was able to perform bilateral synchronized movements and she perceived that her movements were less stiff on the left when aided by this device, but there was no immediate change in pain levels. She was given information regarding the ongoing use of this device and desensitization techniques with instructions to involve the whole length of her left limb when performing these tasks and repeat them 'little and often', ~ 5 – 6 times a day. She was also referred for a 2-week inpatient stay at the hospital in order to receive daily physiotherapy, hydrotherapy and occupational therapy.

Five months after the patient's first presentation, and 3 months after inpatient rehabilitation she was assessed again in the CRPS clinic. She was able to make a fist with her left hand and had noticed a reduction in the frequency of colour and temperature changes. Her pain and function had improved (Brief Pain Inventory on presentation: pain intensity = 5.25, pain interference = 4.5, at 5 months: pain intensity = 4, pain interference = 2). She reported feeling greater 'ownership' of her left arm and it only remained 'alien' around the wrist. There remained some residual oedema around the left metacarpal phalangeal joints and phantom swelling was reported in the wrist, thumb and first finger. This first finger was the only digit to be mis-identified on touch with

TABLE 1. Case study signs and symptoms on presentation in the affected limb

	Signs	Symptoms
Pain	X	X
'Conflict' allodynia	X	
Oedema	X	X
Unilateral temperature changes	X	X
Unilateral colour changes	X	X
Increased nail growth and loss of hair	X	X
Referred sensations	X	
Neglect	X	X
Body perception disturbances	X	
Mis-identification of digits	X	
Reduced range of movement	X	X
Weakness	X	X

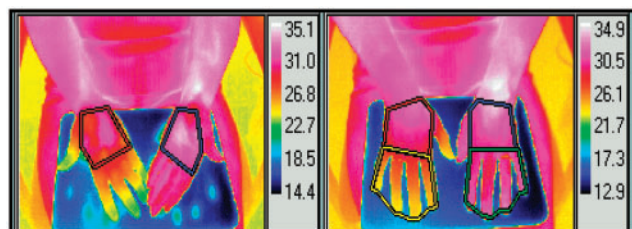


Fig. 1. Thermal images of left and right hands at the time of presentation. Mean temperature values ($^{\circ}\text{C}$) of right (R) and left (L) hands: dorsal R = 29.8, L = 30.9, R-L = -2.1; palm R = 28.9, L = 31.4, R-L = -2.5; fingers R = 23.3, L = 26.6, R-L = -3.3.

the eyes closed. The patient was still aware of occasional sensation in the left side of her face and on examination referred sensations were still present in this region, but other referred sites had been lost. The patient was now able to touch the length of her arm and there was no evidence of conflict allodynia.

The above case report describes, in our opinion, the classic presentation of CRPS type 1 and is highly representative of the type of patient we see in our routine clinics. Although our patient, would meet the proposed revised criteria for CRPS type 1 [19] it is apparent these criteria do not encompass the multiple, more subtle, aspects of this complex condition, some of which are well described in the literature [20–22]. As many of these other signs and symptoms can only be elicited through careful, and often lengthy, examination they may not be detected by the time-pressured clinician, and if mentioned by the patient, do not fit neatly within the necessarily tight diagnostic criteria. It is only when they are viewed in relation to the potential underlying mechanisms that a greater understanding of their significance can be gained for both patient and clinician.

Central mechanism theories in CRPS

Neuropathic pain states, such as CRPS, are defined by the presence of central sensitization, driven by increased nociceptor activity that occurs in the absence of an appropriate stimulus. It has been strongly argued that CRPS is a neurological disease of the central nervous system involving sympathetic, afferent and motor systems [23, 24]. The CNS interacts with the peripheral system via neural and chemical channels and has direct control over the autonomic system thereby giving rise to the clinical anomaly of peripheral vasomotor and Sudomotor changes without peripheral neural damage [23, 24]. Evidence suggests that this interaction between peripheral and central systems arises from a number of sources including sympathetic afferent coupling, reorganization of the central autonomic control, changes in the somatomotor system and peripheral inflammation [24]. This link between neuropathic pain states and inflammation is thought to occur via pro-inflammatory cytokines, derived from cellular elements of the nervous system, that act on other chemokine receptor-bearing neurones, immune cells and glia to increase neurotransmitter activity within the peripheral and central nervous systems [25]. Central theorists propose that the clinical picture of CRPS, with motor, sensory and autonomic changes, arises from a mismatch between the sensory representations and the motor and autonomic representations in the brain which in turn alter the central regulatory mechanisms of the sympathetic, somatomotor and afferent systems (see [24] for review). Where the research is focused in recent years is how this mismatch may arise, be perpetuated and perhaps therapeutically modified with much of this work centred on the motor control system and its interaction with other central mechanisms such as the autonomic nervous system. It is to this body of work that this article will now turn.

The motor control system and the effects of anomalies within it

The role of the motor control system is to enable an individual to perform smooth, coordinated movements and to prepare them for the consequences of that movement. To facilitate this the central nervous systems that generate motor activity are closely coupled to sensory feedback systems and are monitored to detect deviations from that predicted [26, 27]. Frith *et al.* [26] have proposed that from an assimilation of allocentric (external) and egocentric (internal) variables the motor control system 'predicts' a certain response from the sensory system, and 'controllers' within the system compare this desired state with the motor command required to achieve that state. The controllers then produce the appropriate motor commands to achieve the desired outcome.

The prediction, or 'efference' copy, is often only a rough approximation of the actual consequences of a motor command, but it is needed to prepare the system for the consequences of that movement, assess performance if there is a delay in response, differentiate between egocentric and allocentric influences on the system, and maintain a constant update on the interplay between sensory and motor systems. This prediction is then compared with that of actual sensory feedback, and the current state of the system modified accordingly [27].

This sequence of events is processed through a complex interaction between central structures and systems including the visual cortex, basal ganglia, thalamus and somatosensory cortex (see [28] for details). The somatosensory cortex, thalamus and brain stem are vulnerable to remapping following deafferentation or even changing sensory experiences as seen in CRPS and other chronic pain conditions [29–32]. A direct correlation has been demonstrated between the extent of cortical reorganization and the level of pain perceived in CRPS with pain reducing as the changes on the somatopic map start to reverse [33, 34]. Clinically, as our case report demonstrates, these changes are evident in the patient as perceived altered body perception, mis-identification of digits and the presence of referred sensations. Importantly, these clinical symptoms also diminish as pain reduces [17].

Recent research has demonstrated, in those with upper limb CRPS, that similar re-mapping occurs in the primary motor cortex contralateral to the affected limb [35]. However, unlike the reduced representation of the affected hand seen on S1 (the primary somatosensory cortex), the representation of the painful area on the motor cortex becomes enlarged. This has been shown to correlate with poor function in motor planning tasks, particularly those that require integration with visual and proprioceptive cues such as gripping an object [35]. If internal variables become distorted, such as via neural plasticity within the somatosensory and motor cortices, it is easy to see how corrupted efference copies may be generated in CRPS thereby creating a mismatch between expected sensory feedback and the actual one. Our group have demonstrated, in healthy volunteers and those with chronic pain that a range of somaesthetic disturbances can be transiently generated in such a scenario [36, 37]. We have also suggested that as smooth functioning of the motor control system is crucial to the safety of an individual, any perceived abnormality within such a system would alert the autonomic nervous system to prepare for defence strategies via sympathetic stimulation [36]. This may explain how the peripheral symptoms and central changes seen in CRPS are linked and why stress appears to have a direct effect on the frequency and intensity of patient-reported symptoms. Since imagined and observed movements share many of the same processing pathways as actual movements [38], a corrupted prediction of sensory feedback would result in pain and other sensory disturbances in a CRPS-affected limb when intended or attempted movements are performed. This is seen when patients with CRPS attempt to mentally rotate their affected limb into a position determined by a visualized image; they have slower response times than when the activity is imagined with their non-affected limb, and report increased pain and swelling [39, 40]. The clinician will observe that a patient may take time to 'connect' with their affected limb when asked to initiate a movement, and that they report increased levels of pain before any actual movement is observed. Other motor disorders in CRPS include weakness and tremor in the affected limb, slowness of repetitive movements (bradykinesia), dystonias and myoclonus (see [41] for review). The usually flexed postures of a dystonia and the sudden, involuntarily jerk of myoclonus can be particularly distressing to a patient and have a significant impact on their daily function. The frequency of these disorders increases with the duration of the condition [13] and research suggests that central neural networks involved with the inhibition of movement may be dysfunctional at the spinal and cortical levels [41]. The increased difficulty with motor tasks may also contribute to the changes seen in the autonomic nervous

system via the dorsal anterior cingulate cortex. This structure has been demonstrated to modulate an increase in autonomic activity when motor and cognitive activities that require high levels of mental effort are performed [42].

Therapeutic interventions designed to reverse motor–sensory discrepancies have proved beneficial for some [18, 43], but we still have much to learn regarding the optimum frequency and intensity of these interventions in the clinical setting. The patient presented in our case report quickly recognized the benefits of continuing to use her affected limb despite experiencing ongoing pain. Early active use of the affected limb is considered best practice and this may help to not only improve motor–sensory communication but also increase perceived ownership of the limb. Further research in this area is greatly needed.

Access to lower brain perceptions

Although the work described above has shed new light on potential mechanisms in CRPS, there remain many unanswered questions. We still cannot explain why some individuals develop CRPS whilst others do not, though perhaps recent work on the genetics of CRPS may help [44, 45]. There are also the daily, or even hourly, fluctuations in symptoms that perplex the patient and physician and lead to a highly unpredictable course to the condition. Finally, and perhaps the greatest frustration of all, is that CRPS may develop immediately following a relatively innocuous trauma but can take years to resolve, if at all. It is these, and other ongoing puzzlements derived from our detailed clinical histories, that led us to look outside the traditional CRPS literature and seek answers elsewhere. It struck us that some of the symptoms that our patients describe are difficult to understand in the highly evolved animal, such as a desire to amputate a limb or a perception of sections missing from that limb. Therefore, we looked to see if answers may lie in our evolutionary history.

Much of our ‘lower order’ information is lost to us as our evolving brains have developed ‘higher order’ systems by which we interpret our sensory experiences and understand the world around us. Nevertheless, this primitive lower level information is still utilized in certain situations, such as to enable us to make the rapid judgements on the trustworthiness of an individual that are necessary for our safety [46]. When the brain becomes damaged or altered we can get a glimpse into these lower order systems and this can be particularly clearly seen in savants with early infantile autism [47]. These children are highly gifted in such skills as arithmetic or art and their abilities appear ‘superhuman’. For example, a savant child of three can draw a perfectly proportioned, apparently galloping horse, whilst their non-autistic peers are struggling with a misshapen outline [48]. It is thought that such skills are possible as these children are still able to access the basic building blocks by which we construct an exact image or calculate a sum without the overlay of complex conceptualization. For example, we are able to perceive something as three dimensional without being aware of the complex processes involved to arrive at this concept.

What if in CRPS the changes in central mechanisms result in the sufferer having enhanced access to the lower level raw information contained within us all? This may explain the heightened awareness of peripersonal space that we see with conflict allodynia. We use congruent information from vision and proprioception to determine the position of our body in relation to surrounding stimuli but recent research has shown that we can effectively extend the outer limits of our body when using a tool so that the tool becomes a part of us [49]. It is postulated that this ability to expand your peripersonal space evolved so that an organism can act on objects that are not directly within their reach [50]. Perhaps in CRPS the heightened awareness of a need to protect the painful limb results in access to, and operation of, this lower evolutionary pathway and results in an extended peripersonal space that clinically we see as conflict allodynia. However, like the savants,

this access (and hence control) is lost as the central mechanisms revert to normal. The apparently irrational desire for amputation of a CRPS-affected limb and neglect of that limb, may also arise from direct access to previous encryptions for autotomy that were present in our earlier life forms. Likewise, the macro- and micro-somatognosis described by our patients when they close their eyes and describe their affected limbs perhaps gives us an insight into how our evolutionarily earlier limbs were constructed. Clearly, this hypothetical model would need testing. The autistic literature has hypothesized that this could be achieved via using an artificial means to access lower level information, such as inducing an altered state of consciousness [47]. Alternatively, experiments could focus on changes in near peripersonal space as work in those with neglect suggests that the integration of visual–tactile information occurs automatically, below the conscious level, via bottom-up processing [51]. In a subject with CRPS, their response to the threat of touch, close and distant, in the affected and unaffected limbs could be explored and compared with those with resolving symptoms and healthy volunteers. Concurrent imaging data, in line with animal studies [50] would further enhance this experimental model.

In conclusion, the clinical presentation of CRPS may be a confusing picture for both patient and clinician as the range of symptoms displayed is only partially described by the current diagnostic criteria. Recent work on central mechanism theories is starting to help us understand these clinical puzzlements but further work is needed to help us design effective therapeutic approaches. CRPS may be more easily understood if it is viewed as a manifestation of multiple responses to a perceived or actual injury that may include access to earlier evolutionary pathways.

Rheumatology key messages

- Clinical presentation of CRPS is only partially described by diagnostic criteria.
- Central mechanism theories explain some of the bizarre clinical symptoms.
- Access to normally suppressed evolutionary pathways may explain other perceptual abnormalities.

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