COMPLEX REGIONAL PAIN SYNDROME: WHY DOES PAIN SPREAD FROM THE INJURED LIMB TO THE FACE?

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Thesis submitted in fulfillment of requirement for the degree of Doctor of Philosophy

July 2009

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Declaration

This thesis contains no material which has been accepted for the award of any other degree in any other university and, to the best of my knowledge or belief, contains no material previously published or written by another person, except when due reference is made in text.

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July 2009
Abstract

In patients with complex regional pain syndrome (CRPS), sensory disturbances commonly spread outside the affected limb, in particular hemilaterally. Hyperalgesia to pressure-pain was, for instance, documented in the forehead ipsilateral to the affected limb [7]. The aim of this thesis was to investigate potential mechanisms involved in this spread. Firstly, the effect of experimental limb pain (the cold pressor test) on sensory changes to pressure-pain and sharpness outside the immersed limb was investigated on each side of the forehead in samples of 45 and 32 healthy volunteers. Prior to pain induction, differences in pressure-pain or sharpness sensitivity between the left and right side of the forehead were generally small or non-existent. The induction of severe limb pain in healthy volunteers produced a bilateral reduction in forehead sensations to pressure-pain and sharpness with greater analgesia to pressure in the ipsilateral forehead. Central inhibitory pain control mechanisms may have mediated this effect.

The second study attempted to disrupt inhibitory pain control prior to cold-induced limb pain (cold pressor test) in 85 healthy volunteers and investigated the effect of these procedures on sensitivity to pressure-pain and sharpness on each side of the forehead. Optokinetic stimulation was employed to disrupt inhibitory pain control as increased forehead sensitivity was reported following this form of motion sickness-producing stimulation [4; 6]. Sensitivity to pressure-pain and sharpness increased in the forehead after optokinetic stimulation. However, during the subsequent cold pressor test, forehead sensitivity to these stimuli decreased in the most pain sensitive participants, suggesting that inhibitory pain control mechanisms remained intact.

The finding of a previous study that unilateral carrageenan-induced hindpaw inflammation in the rat produces thermal hyperalgesia both in the inflamed hindpaw and
the non-inflamed forepaw, but not in the contralateral paws [16] prompted us to investigate a link between limb inflammation and hemilateral hyperalgesia. Pressure-pain and sharpness sensations were assessed on each side of the forehead in 17 healthy volunteers during 48 hours of topical treatment of the forearm with the inflammatory agent, capsaicin. Capsaicin-treatment evoked a bilateral reduction in forehead sensitivity to sharpness and an ipsilateral reduction in forehead sensitivity to pressure-pain. Differences in the tissue affected (muscle in the rat study and skin in the human study) may explain the differing results from the rat study.

The issue of inflammation-induced hemilateral sensory disturbances was explored further in patients with CRPS. NMDA-receptors are up-regulated in inflamed human skin [15] and appear to be involved in sensitizing primary afferent nociceptors during inflammation and tissue injury [2; 8; 10]. In a double-blind placebo-controlled trial, the NMDA antagonist, topical ketamine, was applied to the affected or unaffected limb of 20 patients with CRPS and the effect on sensitivity to a range of sensory stimuli (touch, pinprick, thermal, pressure, brushing) was investigated in the affected and unaffected limb and on each side of the forehead. Hyperalgesia to sharpness, pressure, cold and heat, and allodynia to brushing, were detected in the ipsilateral forehead before treatment. This was generally associated with heightened sensitivity in the affected limb. The topical application of ketamine reduced allodynia and sharpness hyperalgesia in the affected limb. As allodynia to brushing the skin and sharpness hyperalgesia are mediated by sensitized spinal nociceptive and wide dynamic range neurons that receive input from nociceptive A-delta fibers and non-nociceptive A-beta fibers [12; 13], peripheral NMDA-receptors may play a role in the sensitization of central neurons in CRPS. In some patients with allodynia in the forehead, forehead allodynia was reduced following treatment of the affected limb.
with ketamine, suggesting that a similar mechanism may contribute to the heightened sensitivity in the forehead.

Prior to this thesis, a small number of studies suggested that central inhibitory pain control is disrupted in patients with CRPS [3; 5; 14]. The laterality of such mechanisms, and their potential contribution to hemilaterial hyperalgesia, was explored. CRPS pain increases during startle with a loud tone [3; 5]. Whether this increase in pain to acoustic startle differs between startle in the ipsilateral and contralateral ear was investigated in 28 CRPS patients. Acoustic startle in the ear ipsilateral to the affected limb induced greater limb pain than startle in the contralateral ear. In addition, auditory discomfort was greater to ipsilateral than contralateral ear stimulation and in patients with increased pain to startle than in a small group of non-responders, suggesting not only that inhibitory pain control is disrupted in CRPS but that central neurons both in the somatosensory and auditory systems are facilitated, in particular to stimulation on the ipsilateral side of the body.

The laterality of a dysfunction in inhibitory pain control was explored further by investigating pressure-pain and sharpness sensations on each side of the forehead in 22 CRPS patients during noxious cold stimulation of the affected limb versus noxious cold stimulation of the contralateral unaffected limb. Cold water immersion of the healthy limb decreased forehead sensitivity to pressure-pain bilaterally and decreased clinical pain in the affected limb. In contrast, immersion of the symptomatic limb increased pressure-pain sensitivity on both sides of the forehead. Sharpness ratings in the forehead remained unchanged to immersion of either limb. Nociceptive afferent input from the CRPS affected limb may thus either fail to evoke inhibitory processes or simultaneously evoke a pain facilitatory mechanism that masks inhibitory influences.
Finally, pressure-pain and sharpness sensations were investigated on each side of the forehead in 35 chronic pain patients without CRPS (neuropathic or nociceptive limb pain, back pain or acute herpes zoster/postherpetic neuralgia) and were compared to similar measurements obtained in 34 patients with CRPS. Ipsilateral forehead hyperalgesia to pressure-pain was more common in CRPS patients (59%) than patients without CRPS (14%). Non-CRPS patients mainly reported symmetrical (within normal range) forehead sensations. Ipsilateral forehead hyperalgesia to sharpness occurred in 38% of CRPS patients which was similar to that in patients without CRPS. Nonetheless, symmetrical sharpness sensations dominated in both groups. In general, heightened sensitivity to pressure and sharpness in the ipsilateral forehead was present in patients with greater pain, sharpness hyperalgesia and swelling at the pain site.

In sum, the results of this thesis indicate that ipsilateral forehead hyperalgesia, in particular to pressure-pain, may be specific to CRPS. Nociceptive input from the inflamed CRPS limb may sensitize neurons in the dorsal horn and neurons at supraspinal sites that receive input from the affected limb such as the contralateral thalamus. Hyperexcitability in thalamic nuclei contralateral to the affected limb which receive convergent input from hemilateral body sites could not only explain the presence of hemilateral hyperalgesia but could also explain heightened sensitivity to other forms of sensory input (e.g., auditory input). Failure of inhibitory pain control, in particular to stimulation on the symptomatic side of the body, or a shift toward facilitatory control in mechanisms with a bidirectional role in pain modulation such as the noradrenergic actions from the locus coeruleus, the serotonergic actions from the raphe nuclei or diffuse noxious facilitatory versus inhibitory controls [1; 9; 11; 17; 18] may further promote the transfer of nociceptive messages to
higher brain sites. The ipsilateral noradrenergic actions from the locus coeruleus is a particular candidate for the hemilateral facilitation of nociception in CRPS.
References


Publications

Refereed articles


Submitted articles

Knudsen L, Drummond PD. Limb inflammation produces analgesia to pressure-pain in the ipsilateral forehead of healthy volunteers. Eur J Pain.


Knudsen L, Finch PM, Drummond PD. Failure of inhibitory pain modulation to noxious stimulation of the symptomatic limb, but not the healthy limb, in complex regional pain syndrome. Pain.


These articles are reproduced in the thesis in their full, original state. This accounts for a certain degree of repetition and inconsistencies in reference style.
Author contributions

In keeping with doctorate research regulations, this is a statement of my part in the research work of this thesis. The study design and ideas for Study one, two, three, six and seven were developed in cooperation with Professor Peter Drummond who was my supervisor throughout my PhD. He also provided valuable consultation throughout the studies. I conducted the testing, analysed the results and wrote the first draft of the papers for these studies and was thus assigned first author. Dr Philip Finch was involved in the recruitment and selection process of patients in Study six and seven and together with Peter Drummond provided editorial comment on the papers.

The ideas for Study four and five were brought forward by Philip Finch who was also involved in the recruitment and selection process of patients for these studies. However, I planned the more detailed practical design in cooperation with Peter Drummond. I carried out the assessments of the patients in both studies and analysed the data for Study five. I was also involved in the data analysis of Study four. Parts of the paper for Study four was written by me, and I wrote the first draft of the paper for Study five. Both Peter Drummond and Philip Finch provided input on intellectual and editorial content throughout this process, and both contributed to writing parts of Study four.
Acknowledgements

There are many people that I need to thank for their help and support throughout the completion of this thesis. Firstly I wish to thank my supervisor, Peter Drummond, who was always extremely supportive and challenged my ideas whilst providing invaluable input. His enthusiasm and creative mind was very infectious and meant that more studies were performed than could be included in this thesis.

I also wish to thank Philip Finch, my external supervisor, whose professional caring interpersonal communication with patients is something I admire. Like Peter, Phil was a great mentor and always very supportive of me, especially when the going got hard.

Thanks, of course, to the participants who made these studies possible. Also a thank you to my writing group partners, especially Juanita Miller Berry and Daphne Su, who additionally provided great discussions about the underlying pathology of chronic pain.

I would also like to acknowledge people in my personal life. My parents, Mogens Knudsen and Ingermargrethe Knudsen, who have shown immense support throughout my life, and who have always encouraged me to perform my best. I would not be where I am without you. My partner, Søren Bruhn Ebbesen, who has patiently listened to me ramble about my studies and who supports me in my endeavours. My friends, especially Katey and David Alexander for always being there for me, and Christian Bitz, for his continuous help and support.
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CP in the CP condition.

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**Figure 2** PPTs and sharpness ratings in the forehead ipsilateral and contralateral to the CRPS-affected limb before and for 12 min after cold water immersion of the healthy limb versus the symptomatic limb. During CP of the healthy limb, forehead sensitivity to pressure-pain initially increased (* p < 0.1 compared to baseline) but subsequently decreased (# p < 0.1 compared to baseline). In contrast, forehead sensitivity to pressure-pain increased and persisted immediately after immersion of the symptomatic limb (* p < 0.05 compared to baseline). No changes were observed for sharpness sensations.
Error bars indicate standard errors and the arrow represents the CP.

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noxious inhibitory controls or serotonergic projections from raphe nuclei may explain findings of generalized sensory disturbances in CRPS patients. For clarity, descending influences from the LC are presented schematically.
CHAPTER 1

INTRODUCTION TO COMPLEX REGIONAL PAIN SYNDROME

1.1 The problem of complex regional pain syndrome

Complex regional pain syndrome (CRPS) is a painful condition of the extremities that may develop following traumatic injury (most commonly fractures) or surgery [10; 21; 23; 104]. Although a relatively rare condition (i.e. 20.57-26 per 100,000 person years) [23; 81], the pain and symptoms are usually severe and often spread to other parts of the body [28] resulting in considerable disability [80].

Unfortunately, the condition is not only under-recognised [65] but also difficult to treat because the exact physiological underpinnings of the syndrome are not yet fully understood. This has devastating consequences for the individual CRPS sufferer as loss of employment, domestic and social disruptions, litigation and financial problems usually follow [4; 24; 35; 52]. Depression resulting from social isolation and helplessness add to such problems, in particular in chronic CRPS [24; 78].

Current treatments include medication, sympathetic blocks, sympathectomy, acupuncture, physiotherapy, psychological treatment, peripheral nerve stimulation and spinal cord stimulation with limited success [15; 19; 20; 38; 41; 44; 48; 64; 73; 74; 91-94; 106; 110]. In order to find a successful treatment for CRPS, more research into the physiological mechanisms responsible for the ongoing pain and related symptoms is required. Improving the clinical management of pain through such efforts is an important
step towards minimizing the psychological, physical and financial costs to patients, as well as society.

### 1.2 Diagnosis and clinical features

In 1994, the International Association for the Study of Pain (IASP) introduced the umbrella term CRPS to encompass a number of painful limb conditions with similar etiology. These included amongst others algodystrophy, shoulder-hand syndrome, causalgia and reflex sympathetic dystrophy [6; 14; 71; 85]. This was done in an attempt to clarify and improve clinical recognition and diagnosis of what was believed to be a shared underlying disorder [46]. A set of diagnostic criteria was proposed based on expert advice [91]. These are displayed in Table 1. Extreme pain, hyperalgesia or allodynia along with evidence of autonomic disturbances were considered essential for the diagnosis of CRPS which also required the exclusion of other potential causes for the pain.

<p>| Table 1 |</p>
<table>
<thead>
<tr>
<th>IASP diagnostic criteria for CRPS (criteria 2-4 must be satisfied) [61]</th>
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<tr>
<td>1. The presence of an initiating noxious event, or a cause of immobilization.</td>
</tr>
<tr>
<td>2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.</td>
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<tr>
<td>3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.</td>
</tr>
<tr>
<td>4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.</td>
</tr>
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If no sign of nerve damage, diagnose CRPS I. If major nerve damage, diagnose CRPS II

Two subsets of CRPS, CRPS I and CRPS II, were considered to exist [91]. CRPS II is diagnosed when there is obvious evidence of peripheral nerve lesion clinically (sensory loss, muscle weakness, reflex loss) or during neurophysiological assessment (nerve
conduction, electromyography) [42] whereas type I is diagnosed when no lesion of major nerves is detected [61]. However, as minor nerve damage such as injuries to small distal nerve branches arising from broken bones or dislocations may go undetected [13], the involvement of nerve damage in CRPS I has also been suggested [13; 69]. In support of this, loss of normal C and Aδ fibers [2] as well as abnormalities in C fibers [100] have been detected in CRPS I patients. More recently a study reported a distal degeneration of small-diameter axons (by 29%) in 17/18 CRPS I patients [69], supporting the involvement of minimal distal nerve injury in CRPS I. For such reasons, some researchers and clinicians no longer discriminate between the two subtypes [13]. However, others question such assertions [49; 70; 75]. In this thesis, the general term CRPS will be used mainly for ease of communication and is not a reflection of the author’s stand on this issue.

The diagnosis of CRPS is at present mainly by clinical examination based on the 1994 IASP criteria. Concerns have been raised about this as evaluation of these criteria suggested poor inter-observer reliability [99] and, although they appeared to be quite sensitive at detecting CRPS, they appeared to have low specificity leading to over-diagnosis [17; 33; 40].

Based on a factor and cluster analysis of 123 patients meeting the IASP criteria for CRPS, Harden and colleagues suggested alternative diagnostic criteria which considered both sensory, vasomotor, sudomotor/edema and motor/trophic changes important for the diagnosis of CRPS [40]. The contribution of self-reported symptoms to diagnostic accuracy, in addition to signs detected at physical examination was emphasized [33; 40].

Based on an evaluation of these latter criteria, a consensus group of international CRPS experts meeting in Budapest in 2003 to revise the current 1994 diagnostic criteria proposed two slightly different sets of criteria for CRPS which differed in their research
versus clinical use [45] (Table 2). For clinical purposes, a decision rule requiring two of four neurological sign categories and three of four symptom categories to be satisfied were considered sensitive enough [17] whereas a requirement of four of four symptom categories and two of four sign categories were considered specific enough for research purposes [17; 45]. These changes have been proposed to the Committee for Classification of Chronic Pain of the IASP for inclusion in future revisions of their taxonomy and diagnostic criteria [43].

Table 2

Proposed CRPS diagnostic criteria [40; 45]

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General description of CRPS:
CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

To make the clinical diagnosis, the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event.
2. Must report at least one symptom in three of the four following categories:
   - Sensory: reports of hyperesthesia and/or allodynia.
   - Vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry.
   - Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry.
   - Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).
3. Must display at least one sign at time of evaluation in two or more of the following categories:
   - Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement).
   - Vasomotor: evidence of temperature asymmetry (>1°C) and/or skin colour changes and/or asymmetry.
   - Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry.
   - Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).
4. There is no other diagnosis that better explains the signs and symptoms.

For research purposes, diagnostic decision rule should be at least one symptom in all four symptom categories and at least one sign (observed at evaluation) in two or more sign categories.
1.2.1 Pain and sensory disturbances

The first criterion for a diagnosis of CRPS in both the original IASP criteria and the revised criteria is continuing pain. Nonetheless, some patients may display symptoms consistent with CRPS without pain [30]. Usually, the pain is of greater duration, distribution and severity (typically described as moderate to severe by patients) than what would normally be expected from the inciting injury [57; 59; 76; 80]. A deep pain that is often more permanent than lancinating is generally reported [10; 76]. The pain may be burning, aching, throbbing, tearing, pricking, shooting, stinging, dull or sharp [10; 12; 76; 80].

The pain is usually worsened by additional sensory disturbances in more than 70% of cases [10; 40; 104]. These occur in a variety of combinations and to a variety of stimuli [88]. Hyperalgesia (a heightened sensitivity to painful stimuli) exists in some form in the majority of patients [12; 40; 104]. Hyperalgesia to heat pain, cold pain, pinprick, pressure, pinch and impact stimuli has been documented in the symptomatic limb [10; 28; 47; 53; 76; 77; 87; 88; 90]. Allodynia (pain arising from normally non-painful stimuli) to warm and cool temperatures, touch, vibration, movement and dynamic brushing may also occur [10; 50; 53; 55; 76; 77; 88]. In addition, wind-up related pain from repetitive stimulation may be enhanced in the affected limb [88; 90].

CRPS patients may also experience a loss of sensation. This was found to stimuli such as touch, heat pain, cold pain, warm thresholds and pinprick [10; 28; 47; 53; 87; 104]. Interestingly, these negative disturbances may co-exist with positive sensory disturbances [28; 47; 104]. A feeling of numbness in the limb has also been described [12].
1.2.2 Vasomotor disturbances

Vasomotor dysfunction manifests as changes in skin temperature and red (flushed) or bluish (cyanotic) skin. Altered skin temperature is evident in the majority (60-90%) of CRPS patients [10; 80; 104]. The limb may express itself as warm or cold [80; 88; 104; 108]. The limb appears to be warmer in acute stages and colder in later and chronic stages [9; 10; 47]. However, a warm limb was also found in patients with CRPS for up to 12 years [104] and some patients report decreased skin temperature from the onset of CRPS [18]. Separate warm and cold CRPS phenotypes have been suggested [29]. Regardless of whether hot or cold, the typical temperature difference between the affected and unaffected limb is more than 1.0 °C [57; 108]. Temperature asymmetry has been found to accurately discriminate between CRPS and non-CRPS patients [16; 108; 109]; however, there is debate as to the diagnostic utility of this due to the changing nature of temperature asymmetry within patients [22; 39; 57; 67; 89].

Discolouration of the limb occurs in more than 50% of patients [80; 100; 104]. The affected CRPS limb may appear a purple-bluish or red colour signifying underlying changes in blood flow (vasoconstriction or vasodilatation) [9; 83; 88; 100; 107; 108]. Red skin has been suggested to be more common in acute stages and cyanotic blue skin in chronic stages [10].

1.2.3 Sudomotor disturbances/edema

Edema and changes in sweating are common in CRPS (70-80%) [10; 28; 53; 88; 104]. The majority of patients report swelling in the affected limb. However, this appears to be an intermittent and changing feature [80]. There is evidence of a higher incidence of edema in acute stages [10; 47]. Sweating abnormalities in the affected limb appear to be
less common [8; 51; 80] and may be marked by hyperhidrosis (increased sweating) or hypohidrosis (decreased sweating) [10; 11; 28; 51; 53; 88; 104].

1.2.4  *Motor/trophic disturbances*

Motor disturbances occur in the majority of CRPS patients. Most predominant is a decreased range of movement and weakness in the affected limb which occurs in 80-90% of patients [10; 76; 100; 104]. Other motor disturbances may be present in various combinations. They include paresis, myoclonic jerks or muscle contractions, muscle spasms, tremor, exaggerated tendon reflexes, muscular incoordination, bradykinesia (slowness of repetitive movements), and, less common, dystonia [7; 10; 27; 36; 57; 60; 66; 76; 80; 86; 87; 98; 101; 102; 104]. In addition, some patients report a neglect-like phenomenon [32; 34; 57] with difficulty initiating movement and with feelings of the symptomatic limb as foreign or strange or larger than its actual size [31; 58; 63].

Trophic changes may also accompany CRPS and does so in 20-50% of cases [80; 104] possibly as a consequence of disuse [46]. Increased hair growth (hypertrichosis) and hair loss (hypotrichosis) of the affected limb have been documented [51; 53; 88; 104]. Nails of the affected extremity may also become brittle and display changes such as discolouration, breakage, increased or decreased growth [51; 53; 68; 88; 95; 103; 104]. Increased hair and nail growth seems to occur early on in the disorder and to be replaced later by reduced hair and nail growth as well as atrophy of the skin [12]. Skin atrophy may present as coarsening, thickening or thinning of the skin with a brown-grey scaly pigmentation or shiny appearance [53; 100; 104]. In severe cases, atrophy of the muscles with fibrosis may also be experienced [88; 100]. Although osteoporosis is not described as
an essential component of CRPS, a number of studies have demonstrated patchy osteoporosis in CRPS [37; 54; 56; 62; 82; 111].

1.3 Spread of symptoms

The symptoms of CRPS may be limited to the affected area in a cuff-, glove- or stocking-like distribution or may be limited to the glabrous skin of hands or feet [10]. However, the spread of CRPS pain and symptoms to other parts of the body has been widely documented [5; 25; 26; 28; 54; 55; 59; 76; 77; 86; 97; 104; 105]. CRPS pain may even present itself remote from the injured area (e.g., after myocardial infarction) [1].

A number of studies have demonstrated CRPS symptoms in more than one limb, in rare cases in all four limbs [3; 5; 7; 59; 72; 79; 84; 86; 90; 96; 102; 104; 105]. These studies were all largely based on subjective patient reports as to the areas of the body affected by CRPS. Maleki and colleagues [59] mapped the spread of CRPS in 27 patients and suggested three types of spread: contiguous spread (enlargement of the affected area), independent spread (to an area remote from the initial area i.e., from an arm to a leg) and mirror spread (to the contralateral limb).

More recently it has become clear that even when no subjective reports of a spread of CRPS are sought from patients, sensory disturbances can be detected outside the primary CRPS area. Quantitative sensory testing by Rommel and colleagues [76; 77] found hypoalgesia on the entire ipsilateral side of the body or in the ipsilateral upper quadrant in 50% of CRPS I patients. This was demonstrated both to pinprick, touch and thermal thresholds. Thimineur’s group [97] similarly detected hypoalgesia to thermal stimuli and motor weakness ipsilateral to the affected limb in half of their CRPS participants. These participants, in addition, exhibited bilateral sensory and motor deficits in comparison to
controls or CRPS patients without hemilateral differences. Nonetheless, the deficits were more pronounced ipsilaterally.

More recently, findings of hemilateral involvement were confirmed by Drummond and Finch [28]. A loss of sensitivity to touch in the affected limb was found to be associated with diminished sensitivity to sharpness, cold and heat-pain in the ipsilateral forehead. In addition, hemilateral hyperalgesia was reported in 78% of patients. Most marked was the finding of lower pressure-pain thresholds on the side of the forehead ipsilateral to the affected limb compared with the contralateral forehead, suggestive of ipsilateral mechanical hyperalgesia. In addition, sharpness sensations to pinprick were associated with similar sensations in the affected limb. Huge et al. [47] have since discovered cold hyperalgesia both in the affected and contralateral unaffected limb in acute and chronic CRPS compared to controls. Interestingly, hyperalgesia to heat was also detected bilaterally in acute CRPS but was evident only in the symptomatic limb in chronic CRPS.

From these studies, it is clear that CRPS is commonly marked by a spread of sensory disturbances outside the injured area that typically extends ipsilaterally. The cause of this spread is unknown. Is it simply a result of pain in a limb? Is it the result of anomalies in central pain modulation? Do neurogenic inflammation or central sensitization, that seem to accompany CRPS, contribute to this spread? Determining the underlying mechanisms of the spread in CRPS is important if we are to find appropriate treatments to deter this debilitating development in patients. The current thesis seeks answers to the above questions in an attempt to bring us closer to an understanding of the underlying mechanisms of spread of sensory disturbances in CRPS.
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CHAPTER 2
NORMAL PAIN PROCESSING

2.1 Pain and its function

The International Association for the Study of Pain (IASP, p. 250) [78] defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” The IASP definition refers mainly to acute pain which is associated with injury and many diseases. Acute pain serves an important function. It signals to the brain that real or potential tissue injury is taking place and induces withdrawal or escape as a protective response [43]. Or, in the case of sickness, hyperalgesia and allodynia is associated with inactivity and increased sleep probably to help conserve energy to assist recuperation [68; 112]. On such grounds, it has been argued that the ability to experience pain evolved because it was adaptive and increased the probability of survival [30]. However, in CRPS, where pain persists beyond tissue healing and develops into a chronic and debilitating state, pain can hardly be considered beneficial.

2.2 Nociception

The early idea that the transmission of pain occurs through a single pathway from the skin to the brain has long been refuted. Instead pain processing is a rather complex process involving both the peripheral and central nervous systems [44].

2.2.1 Peripheral nociception

The first step in the pain process is the detection of a painful stimulus in the periphery by primary afferent fibers. Neurons responding to noxious stimuli in the
periphery contain small-diameter thinly myelinated fast conducting Aδ fibers or small diameter unmyelinated slowly conducting C fibers [8]. These mediate respectively ‘first’ (rapid, acute, sharp, well-localised) and ‘second’ (delayed, dull, burning, diffuse) pain [8; 21; 83]. Aδ fibers respond to intense mechanical stimuli [83] and extreme thermal stimuli (<5°C or >45°C) [8] whereas many C fibers are polymodal and respond both to noxious thermal (41°C to 49°C), mechanical and chemical stimuli although some seem to respond to heat only [21; 83]. C fibers are considered more common than Aδ fibers [21]. An additional class of nociceptors are the so called ‘silent’ nociceptors which seem to respond only when they have become sensitized by tissue injury or inflammation [87]. Finally, peripheral neurons responding to innocuous (non-painful) stimuli contain large diameter myelinated fast-conducting Aβ axons [83]. The free nerve endings of all these fibers are distributed throughout the skin and deep tissues [8].

When the primary afferent fibers are activated, action-potentials are generated which travel along the afferent axons to the dorsal horn of the spinal cord [8]. In the dorsal horn, the fibers synapse either directly or indirectly (via interneurons) with second-order projection neurons via the release of a number of neurotransmitters such as the excitatory amino acid glutamate or the peptide substance P [43; 175]. The cells of the dorsal horn contain specific receptors for these substances such as the receptor for glutamate, the N-methyl-D-aspartate (NMDA) receptor [21]. The transmission of action-potentials to dorsal horn neurons contains a range of information including the onset, intensity, quality, location and duration of the peripheral noxious (painful) stimulus [8].

2.2.2 Central nociception

The dorsal horn of the spinal cord is an important site for the further processing of nociceptive information. It is separated into various layers (laminas). Most of the neurons
that respond to direct input from Aδ and C fibers are located in the superficial dorsal horn (laminas I and II) [8; 21; 125]. Lamina I contains mostly nociceptive-specific neurons that project to higher brain centers whereas lamina II (the substantia gelatinosa) contains almost exclusively interneurons (inhibitory and excitatory neurons) which respond only to nociceptive input although some also respond to non-noxious stimuli [8]. Wide dynamic range neurons which are activated by input from Aβ, Aδ or C fibers (directly or via excitatory interneurons) are primarily located in lamina V (some in lamina I) [8; 54]. Neurons in ventral horn lamina VII and VIII similarly receive noxious input, but via more complex processes. Interestingly, many lamina VII neurons respond to stimulation of either side of the body unlike most dorsal horn neurons which receive input from only one side [8].

Segmental and widespread modulation of nociception occurs in the dorsal horn and influences the perception of pain. Descending influences in the dorsal horn may emanate from a number of brain sites and occurs via the dorsolateral funiculus pathway [21]. The modulation of nociceptive input in the dorsal horn may be inhibitory or facilitatory depending on the mechanisms and receptors activated. Major pain modulatory mechanisms include gate control, diffuse noxious inhibitory controls (DNIC), coeruleospinal pain modulation, stress-induced analgesia (SIA) and stress-induced hyperalgesia. In addition, peripheral and central sensitization promotes the transmission of pain to higher centers. Nociceptive signals are transmitted from the dorsal horn to the brain via the spinothalamic, spinohypothalamic and spinoreticular tracts [21]. The thalamus, in particular, plays an important role as a processing and relay station for nociceptive input from the dorsal horn to other brain sites such as the somatosensory cortex and the limbic system which are involved in, respectively, the discriminatory and emotional aspects of pain [21].
The transmission of pain from the head and neck has many of the same characteristics as the dorsal horn nociceptive system [21]. The face is densely innervated with primary nociceptive afferent fibers that originate primarily from cranial nerve V and from cranial nerves VII, IX, and X as well as from the upper cervical spinal nerves [21]. The cranial nerve fibers project mainly to nuclei of the trigeminal system whereas the upper cervical nerves project to second-order neurons in the dorsal horn of the spinal cord [21]. Ascending pathways from trigeminal nuclei include the dorsal and ventral trigeminothalamic tracts that terminate in the thalamus [21].

2.2.3 Pain modulation mechanisms

Gate control of nociceptive input. The perception of pain can be reduced by stimulation of the painful area with innocuous stimuli such as ice, vibration, mild transcutaneous electrical nerve stimulation (TENS) or passive movement [52; 85; 119]. The mechanism proposed to underlie this is the competitive balance between dorsal horn input from activity in large diameter non-nociceptive Aβ fibers and activity in small diameter Aδ and C nociceptors [120; 125]. The relative increase in large diameter input suppresses pain [7]. The theory is based on findings that non-nociceptive large diameter afferents inhibit activity of neurons in lamina V (wide dynamic range neurons) by activating inhibitory interneurons in lamina II, and that nociceptive small diameter afferents excite lamina V neurons and inhibit the activity of inhibitory interneurons in lamina II [8]. This opening of the gate for pain by Aδ and C fibers and the closing by Aβ fibers is referred to as the gate control mechanism of pain. The mechanism accounts for localized pain control in that the area of the body in which pain is modulated is linked anatomically to the segments of the dorsal horn where the nociceptive and non-nociceptive afferents terminate [8].
Diffuse noxious inhibitory controls (DNIC). Remote heterotopic analgesic effects have been demonstrated to a range of noxious conditioning stimuli in humans (e.g., thermal, mechanical, electrical, ischemic and chemical (capsaicin) stimuli) [4; 5; 20; 42; 51; 61; 63; 84; 91; 96; 106; 107; 134; 135; 137; 171; 177; 184; 187]. Complementary studies in animals suggest that noxious stimulation selectively inhibits activity in spinal [24; 25; 100; 127; 148] and trigeminal wide dynamic range neurons outside the area of segmental excitation [45; 76; 129]. Such inhibitory effects have been termed counterstimulation or diffuse noxious inhibitory controls (DNIC) and are activated by Aδ and C fibers [104]. Transection of the spinal cord in animals deters this effect, suggesting the involvement of a supraspinal loop [24; 99; 127] with ascending and descending pathways in the ventrolateral quadrant and the dorsolateral funiculus respectively [40; 173]. A reduction in DNIC following lesioning of the subnucleus reticularis dorsalis in the caudal medulla suggests the involvement of the medulla in this loop [19; 102; 174]. Serotonin and endogenous opioids are believed to at least partly mediate the descending control in DNIC [32; 41; 46; 103; 186]. However, lesions of the rostral ventromedial medulla (RVM), the main distributor of serotonin in the central nervous system, and lesions at brain sites involved in opioid-mediated stress-induced analgesia such as the periaqueductal gray (PAG), do not modify DNIC [102]. See section on stress-induced analgesia, page 28. Thus, although there seems to be some convergence at the level of neurotransmitter/neuropeptides between these endogenous analgesia mechanisms, DNIC can be considered a neuroanatomically separate mechanism [23].

The DNIC effect is, as the name implies, diffuse, affecting both sides of the body. Bilateral DNIC effects were detected by recordings from spinal and trigeminal convergent neurons in rats following immersion of the paws, tail and muscle in hot water [18; 19]. To the best of my knowledge, bilateral DNIC effects have been assessed in humans in only one
study. Pain sensitivity was reduced to a similar extent in the left and right thigh during tourniquet-induced left arm pain [171].

More intense conditioning stimuli induce greater DNIC effects [58; 101; 172; 174; 184] but whether the extent of DNIC is related to the perception of pain is less clear with research providing support both for and against an association [5; 62; 98; 140]. Some research even suggests that pain is not necessary for the induction of DNIC [92; 97; 98].

**Coeruleospinal pain modulation.** The nucleus locus coeruleus (LC), located in the dorsolateral pons, may induce antinociception when stimulated electrically or chemically [81; 113; 180]. It is thought to inhibit nociceptive activity in the dorsal horn [33; 72; 82; 126] and the trigeminal subnucleus caudalis [168] via noradrenergic projections [57; 71; 181] that act on \( \alpha_2 \)-adrenoceptors [81; 82].

Electrical stimulation of primary afferent A\( \delta \) fibers produces excitation of descending noradrenergic neurons from the LC, resulting in an increase in the level of noradrenaline in the dorsal horn [71]. Inhibitory influences projecting from the LC have also been associated with stress-producing stimuli [10] and inflammation [115; 166-169]. The PAG may activate noradrenergic projections from the LC via opioidergic mechanisms (directly or via the RVM [125]) or via substance P containing fibers [139; 192].

Projections from the LC appear to be bilateral [34; 35; 150; 170] and to involve all segments of the spinal cord [138]. Injection of anterograde transport of Phaseolus vulgaris leucoagglutinin (PHA-L) in the LC resulted in consistent labeling in cervical, thoracic and lumbar segments of the spinal cord [138]. Interestingly, more recent studies have found that activation of the LC during unilateral carageenan-induced hindpaw inflammation is evident only in the ipsilateral dorsal horn and not the contralateral dorsal horn [163-165; 167]. In addition, measurements of response thresholds to thermal stimuli on all four paws of the rat
during unilateral hindpaw inflammation found shorter paw withdrawal latencies of the inflamed hindpaw as well as the non-inflamed, but hyperalgesic, ipsilateral forepaw in rats with bilateral LC lesions than in sham operated rats [169]. This was not observed in the contralateral hind- or forepaw, suggesting that the LC may inhibit nociception hemilaterally. The findings of a bilateral increase in Fos expression during unilateral hindpaw inflammation [166], and that unilateral lesions of the LC either contralateral or ipsilateral to the inflamed paw do not alter the inhibitory influences from the LC [111], suggests that the ipsilateral activation originates bilaterally, but perhaps travels through the dorsolateral funiculus ipsilaterally [111].

Noradrenergic projections from the locus coeruleus may also facilitate nociception [70]. This effect appears to be mediated by $\alpha_1$-adrenoceptors, rather than $\alpha_2$-adrenoceptors [22; 53; 70; 132]. In addition, coeruleospinal action at $\alpha_1$-adrenoceptors in the RVM may activate ON-cells that facilitate nociception both in the spinal cord and the trigeminal nucleus caudalis [55; 121]

*Stress-induced analgesia (SIA).* A stressor can be defined as anything that poses a real or perceived threat to a person’s homeostasis [191]. In animals an increase in pain-threshold (SIA) has been documented to a variety of stressors including inescapable foot shock, forced swims, food deprivation and immobilization/restraint [1; 2; 12-16; 31; 48; 59; 65; 66; 110; 151; 159]. In humans, analgesia was documented following exposure or re-exposure to stimuli such as repeated cold pressor stimulation, noxious hand or foot shocks, anticipation of an aversive event, startle with a loud tone and during mentally stressful tasks (e.g., mental arithmetic) [6; 49; 56; 143; 176; 183; 185].

Multiple mechanisms seem to underlie SIA. The most well-documented is the endogenous opioid system [17; 31; 110; 144; 151]. Serotonergic release (5-
hydroxytryptamine or 5-HT) from raphe nuclei such as the RVM during stress, is also associated with SIA [23; 75; 131; 146]. Other neurotransmitters/neuropeptides thought to be involved in SIA include GABA, glutamate and endocannabinoids as well as the former mentioned noradrenergic release from the LC (see section on coeruleospinal pain modulation, page 27) [23; 125].

The descending inhibitory pathway that mediates SIA appears to originate in neurons in higher brain regions such as the cortex [118], hypothalamus [124] and amygdala [179], the amygdala being a region that is particularly activated by stress/fear [105]. Neurons from these regions project to brain stem sites such as the PAG and raphe nuclei which in turn project to the dorsal horn [23; 123; 182].

The intensity, duration and type of stressor may determine the type of SIA as well as the degree of the subsequent analgesia. The sequential exposure of rats to a series of inescapable foot shocks, for instance, resulted in both an early naltrexone-insensitive and a late naltrexone-sensitive analgesia [48]. Naltrexone is an opioid receptor antagonist [2]. In a forced swim, SIA increased with more extreme temperatures [38], and the degree of SIA differed with the frequency and pulse-width of electric foot shock [188].

Under some experimental conditions, stress can even induce hyperalgesia instead of analgesia (stress-induced hyperalgesia) [108]. Brief or prolonged stressors such as horizontal oscillations or exposure to ether vapours, exposure to a novel or cold environment, acute or chronic restraint, and repeated swim stress produced hyperalgesia in animals [59; 69; 88; 93; 141; 147; 154]. Increased pain sensitivity has also been observed in humans to stress and, in particular, anxiety-producing stimuli (e.g., public speaking, academic examinations, the Stroop test, Velten-style emotion induction, shock threat, repetitive shocks and noxious electrical stimulation) [27; 109; 122; 143; 157].
The mechanisms underlying stress-induced hyperalgesia are poorly understood. Activation of serotonergic receptors may produce hyperalgesia instead of analgesia depending on the receptor subtype activated [125] and serotonin was shown to play a role in stress-induced hyperalgesia [79; 114]. On such characteristics, it mimics the bidirectional actions of noradrenaline [125] which similarly has been postulated to play a role in the facilitation of pain during stress [141]. Serotonergic receptor types 5-HT_2, 5-HT_3 and 5-HT_4 enhance neuronal activity whereas receptor types 5-HT_1A and 5-HT_1B suppress neuronal activity [125]. The location of the 5-HT receptor in the dorsal horn, i.e. on excitatory versus inhibitory interneurons or projection neurons, may further determine the resulting outcome [125].

Overactivation and desensitization of opioid receptors was suggested to contribute to hyperalgesia during prolonged stress as naloxone, an opioid antagonist, and ketamine, an NMDA antagonist, deterred repeated swim-stress hyperalgesia [154]. Tolerance to the analgesic effects of opioids is associated with hyperalgesia and increased activity of NMDA receptors [116; 117; 162].

*Peripheral sensitization and inflammation.* Upon tissue damage, additional facilitatory processes are activated [89]. Tissue inflammation, mechanical tissue damage, mild burn injury and treatment with algesic chemicals such as capsaicin, bradykinin, serotonin and mustard oil produce hyperalgesia at the site of injury or stimulation (primary hyperalgesia) [9; 39; 67; 87; 89; 90; 94; 95; 145; 158; 161]. This hyperalgesia is the product of the release of a wide array of inflammatory mediators. These include hydrogen and potassium ions (cells), bradykinin (plasma), serotonin (platelets), histamine (mast cells), TNF-α (mast cells), cytokines (macrophages), nerve growth factor (keratinocytes), endothelin-1 (inflammatory cells, keratinocytes), prostaglandins and leukotrienes (via the
In addition, nociceptors are activated and release a number of neuropeptides, most importantly substance P and calcitonin gene-related peptide (CGRP) adding to the chemical soup [153; 155].

Some of these inflammatory mediators (bradykinin, histamine, substance P) activate nociceptive terminals directly [152] whereas others (prostaglandins, leukotrienes, potassium ions, nerve growth factor, endothelin-1, TNF-α) sensitize nociceptive terminals [11; 128; 133]. This sensitization is associated with changes both in the firing thresholds, kinetics and the excitability of peripheral nociceptors, causing them to fire more readily [43] and may also include the activation of silent nociceptors responsive only to chemical or inflammatory stimuli [160]. NMDA-receptors are furthermore up-regulated in inflamed human skin [156] and appear to be involved in sensitizing primary afferent nociceptors [26; 50; 80].

The pain and primary hyperalgesia resulting from the increased activation and sensitization of nociceptors during tissue damage is restricted to the site of inflammation [39; 87; 90; 94; 142] which furthermore exhibits rubor and calor (redness and heat from vasodilatation), tumor (swelling from leakage of plasma proteins and fluid into the tissue), and function laesa (loss of function) [74; 153]. In addition, secondary hyperalgesia of the surrounding tissue can be observed signifying central sensitization [43].

Central sensitization. In response to continuous C fiber input to the superficial layers of the dorsal horn, such as during inflammation, the activation threshold of dorsal horn neurons decreases and their receptive fields and responsiveness increase [37]. This is referred to as central sensitization and has been demonstrated to a number of stimuli including electrical stimulation, burn injury, experimental inflammation and noxious pinch [28; 29; 37; 73; 77; 86; 148; 149; 189; 190].
The increased excitability from the periphery results in the recruitment of previous subthreshold input to dorsal horn neurons and is probably mediated by NMDA receptor activation [21]. These changes are not restricted to the activated synapses, and prolonged excitation of central neurons causes them to become more responsive to all subsequent afferent input [43]. This explains the pain produced after peripheral injury or inflammation to input from normally non-painful stimuli (alldynia) as well as the spread of pain hypersensitivity to areas outside the tissue injury (secondary hyperalgesia) [43].

Central sensitization manifests within seconds of an appropriate stimulus and can outlast the stimulus for several hours [189] and may not be confined to the dorsal horn but has also been reported in spinothalamic neurons [47; 86] as well as the rostroventral medulla, anterior cingulate cortex and amygdala [130; 136; 178].
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CHAPTER 3
CRPS PATHOLOGY

The exact underlying pathology of CRPS is yet to be elucidated. However, current evidence points to disturbances both in peripheral and central systems. Whether such disturbances contribute to the spread of pain and sensory disturbances in CRPS is unclear.

3.1 Peripheral pathology

3.1.1 Peripheral sensitization and exaggerated inflammation

The appearance of a painful, red, swollen and hyperthermic limb in CRPS is consistent with inflammation, in particular in the acute stages [56]. In addition, the presence of hyperalgesia to heat [56] as well as to pinprick and blunt pressure [102] is suggestive of peripheral sensitization [5].

For such reasons, the involvement of an exaggerated inflammatory response to trauma or surgery has been suggested [12; 13; 64; 116; 120]. Indicators of inflammation in the affected limb include increased levels of pro-inflammatory mediators such as bradykinin, IL-6, TNF-α and endothelin-1 [14; 50; 55; 74; 107; 120] as well as increased vascular permeability for macromolecules [84]. In addition, skin lactate levels are high [7] and oxygen consumption is low, consistent with inflammation [54; 64].

As inflammation in the classical sense (i.e., immune-induced inflammation) has not been documented [10; 20; 90; 108], a chronic release of neuropeptides from primary afferent fiber terminals (neurogenic inflammation) was suggested to underlie the inflammatory response in CRPS [12; 13; 64; 119]. As mentioned earlier, neuropeptides such as CGRP and substance P are released from the endings of primary afferent fibers
during trauma-related activation and sensitization [104; 105], and cytokines increase the neuropeptide release of these afferents [83].

In support of exaggerated neurogenic inflammation, CGRP and substance P was significantly increased in serum samples from the CRPS-affected limb [11; 96]. Furthermore, when nerve fibers were stimulated by transcutaneous electrical stimulation greater protein extravasation (mediated by substance P) and vasodilation (mediated by CGRP) were seen in patients than controls both in the affected and unaffected limb [11; 119]. Similarly, perfusion of substance P through dermal microdialysis fibers showed that substance P was significantly more effective at inducing plasma protein extravasation in CRPS patients than controls [64]. Again this response was evident both in the affected and unaffected limb. On the basis of such findings, it was suggested that an increase in neuropeptide release from primary afferent fibers in combination with a diffuse impaired inactivation of neuropeptides is present in CRPS [12]. Consistent with this, lower levels of anti-inflammatory mediators such as IL-4 and IL-10 were detected in CRPS compared to controls [107]. Perhaps this combination produces an ongoing cycle of inflammatory mediator release and activation/sensitization of primary afferents [13]. As neuropeptides are not only released in the periphery but also from the central endings of primary afferents [12], their release could contribute to central sensitization [12]. The presence of increased pro-inflammatory cytokines has been documented in CRPS cerebrospinal fluid [1; 2]. A very recent study additionally found microglial and astrocytic cell activation in spinal cord tissue from a patient with longstanding CRPS who died from cardiopulmonary arrest [27], consistent with spinal inflammation.

Besides the classical symptoms of inflammation present in CRPS, neurogenic inflammation could explain the presence of other CRPS symptoms [13]. The release of
CGRP in CRPS may, for instance, explain the increased sweating [97] and increased hair growth in the affected limb [13; 51]. In addition, TNF-α and substance P activate osteoclasts and may account for the high turnover osteoporosis in CRPS which is marked by increased osteoclastic activity [13; 66]. Although the presence of a cold limb may seem inconsistent with inflammation, increased levels of the inflammatory mediator endothelin-1, which is produced by the endothelium and is a potent vasoconstrictor, were found in cold extremity CRPS [13; 50].

3.1.2 Sympathetic nervous system dysfunction

Under normal circumstances, the sympathetic nervous system (SNS) is not directly involved in nociception [6; 32; 38; 39]. Aδ fibers and C fibers are not activated or sensitized by sympathetic activity [38; 39; 57]. In CRPS, however, sympathetic arousal following startle with a loud tone was shown to increase spontaneous pain [32]. Also, activation of the SNS during whole body or forehead cooling increases pain and the spatial distribution of mechanical dynamic and punctuate hyperalgesia [6; 32]. Another argument for the involvement of the SNS in CRPS is the reduction of pain and hyperalgesia following sympathetic block [22; 88; 95; 98; 106] which is rekindled following intradermal injection of adrenergic agonists into the sympathectomised limb [3; 106] or by stimulation of the SNS [6; 32]. However, sympathetic block is only effective in a subgroup of patients (who are subsequently considered to have sympathetically maintained pain (SMP)), and randomized placebo controlled trials suggest no efficacy of sympathetic block over placebo in unselected groups of CRPS patients [69; 98].

The mechanism underlying the interaction between sympathetic activity and pain and hyperalgesia in CRPS is unclear. Direct or indirect coupling between sympathetic
efferents and nociceptive afferents has been suggested [12; 47; 58; 95]. In support of this, electrophysiological recordings in a human with SMP showed the direct activation of nociceptive fibers by increased endogenous sympathetic activity and by intradermal injection of noradrenaline [60]. The activated fibers appeared to be mechano-insensitive nociceptors which are known to be associated with pain and hyperalgesia as well as neurogenic inflammation. Findings such as increased excitability in dorsal root ganglion neurons to phenylephrine ($\alpha_1$-agonist) in vitro [87], in addition to close physical association between sympathetic neurons and sensory neurons in nerve bundles and near blood vessels in the upper dermis of normal human and rat skin [47], support the possibility of a close link between sympathetic efferents and nociceptive afferents.

The sympathetic response in CRPS does not involve sympathetic overflow as initially thought; in fact lower levels of noradrenaline rather than increased levels were demonstrated in the CRPS limb [21; 28; 93; 115]. Hence, it was suggested that decreased noradrenaline levels result in increased sensitivity (supersensitivity) of $\alpha$-adrenoceptors or the direct expression of these on nociceptive afferents [33]. Neurogenic inflammation was suggested as a possible co-contributor to such changes [12; 47; 58]. Sprouting of new sympathetic nerves in the dorsal horn [89] or in the upper dermis of the skin [94] may be triggered by inflammatory mediators [118]. Moreover, the density of $\alpha$-adrenoceptors is increased in sensitized skin from CRPS patients [29]. Consistent with this, transcutaneous iontophoresis of noradrenaline (the sympathetic neurotransmitter) and tyramine (which augments the release of noradrenaline) into healthy skin, sensitized by the inflammatory agent capsaicin, exacerbate thermal hyperalgesia independent of reduced regional blood flow resulting from vasoconstriction [30; 31; 42]. In addition, pharmacological depletion of neural noradrenaline stores induces adrenergic supersensitivity and increases thermal
hyperalgesia in similarly sensitized skin [68]. Noradrenaline may contribute to pain and inflammation by increasing the turnover of inflammatory mediators and algesic substances such as nerve growth factors and prostaglandins [49] or may directly trigger neuropeptide release from nociceptive neurons by activating α-adrenoceptors on nociceptive afferents [67] thus contributing to peripheral sensitization [47; 58]. Perhaps inflammation unmasks latent α-adrenoceptors on nociceptors [47]. Alternatively, α-adrenoceptors may not be expressed on nociceptive fibres but on closely associated cells capable of activating nociceptive fibers such as Schwann cells [47]. Spinal cord glia have been implicated in the generation and maintenance of chronic pain [117]. Interestingly, sweating and trophic disturbances including the presence of a cold limb [13] which have long been considered the result of sympathetic nervous system activity [25] can be explained as neuropeptide effects [12]. A further hypothesis about the generation of pain by the sympathetic nervous system in CRPS is that reduced sympathetic activity, perhaps along with chronic neurogenic inflammation, may contribute to pain and hyperalgesia by causing extreme vasoconstriction [34; 82] thus producing painful hypoxia and acidosis in the affected area [8; 9; 12; 54; 109].

3.2 Central pathology

The appearance of pain and hyperalgesia outside the territory of a single peripheral nerve in CRPS suggests changes within the central nervous system [35; 58; 73].

3.2.1 Central sensitization

Sustained C fiber activation such as peripheral sensitization in response to inflammation leads to increased responsiveness of neurons in the spinal dorsal horn (central
sensitization) [24] and is assumed to underlie the hyperalgesia and allodynia of CRPS [58; 63; 91; 120; 121], although this has not been well studied [25]. As mentioned earlier, in particular the NMDA receptor appears to play a role in central sensitization [15]. One indicator of central sensitization in CRPS is that NMDA-receptor antagonists such as memantine and ketamine appear to be effective at relieving pain and motor symptoms [48; 62; 101; 103], although double-blind placebo controlled trials are missing. In CRPS, central sensitization may be induced and maintained by inflammation, peripheral sensitization and sympathetic activity.

3.2.2 Central disinhibition

Central disinhibition may also contribute to sustaining central sensitization. A lack of DNIC is apparent following noxious forehead cooling which increases CRPS pain rather than reducing it [32]. In addition, CRPS pain is increased during startle with a loud tone whereas startle decreases thermal hyperalgesia in capsaicin-sensitized skin in healthy controls, suggesting that stress-induced analgesia is ineffective in CRPS (although this might alternatively imply adrenergic supersensitivity, see section on sympathetic nervous system dysfunction, page 55) [32]. In a very recent study, Seifert et al. [100] stimulated CRPS patients and controls with repetitive noxious electrical stimulation and showed that inhibitory control was decreased both in the affected and unaffected limb in comparison to controls. In addition, facilitatory control was upregulated in the affected limb compared to the contralateral limb and controls. On this basis, they suggested that continuous peripheral nociceptive input decreases the inhibitory capacity in CRPS patients, or that a general lack of inhibitory pain control is a pre-emptive factor in the development of CRPS. An alternative suggestion was a combination of the two [100]. In any case, a lack of inhibitory
control probably results in unchecked neuronal sensitization. Interestingly, SPECT-scanning in CRPS revealed high activity in the contralateral thalamus in the acute stages of the disease [43]. As the thalamus is highly involved in nociceptive processing, this was suggested to reflect activation of normal pain inhibitory mechanisms [34]. In the later chronic stages of the disease, activity of the contralateral thalamus decreased [43] which may indicate a fatigue or failure of modulatory mechanisms.

3.2.3  **Cortical changes**

Cortical changes in CRPS are thought to reflect central sensitization [73]. Primary somatosensory cortex activation to tactile stimuli in the allodynic limb is enhanced compared to stimulation in the unaffected limb, consistent with central hyperexcitability [61; 71; 111]. The somatotopic map within the primary somatosensory cortex contralateral to the affected limb was also shown to be reorganised in CRPS with shrinkage of the area representing the affected limb as well as a shift of the affected hand towards the lip [61; 71; 85]. In some [71; 85], but not all studies [61], the extent of this cortical reorganization was associated with the intensity of pain and mechanical hyperalgesia and hence attributed to central sensitization. Juottonen and colleagues [61] suggested that disuse due to severe pain may mediate the effect on cortical organisation. Interestingly, cortical reorganisation was reversed during recovery from CRPS [72; 86].

Changes in cortical organisation in response to central sensitization may explain the presence of referred sensations in CRPS [75; 77] as the intensity of referred pain was found to be related to the presence of mechanical hyperalgesia [75]. Cortical changes may also account for the impaired self perception of the affected limb in CRPS [41; 75] and hemilateral sensory deficits [75; 76], although research is yet to confirm this.
Changes in the motor cortex have also been described. Both a reduction and an enlargement of the motor cortical representation of the affected limb have been reported [65; 76]. Such changes correlate with the extent of motor dysfunction [65; 76]. Similar to changes in the somatosensory cortex, hyperexcitable central neurons may underlie these changes. Consistent with this, transcranial stimulation revealed hyperexcitability of the motor cortex of CRPS patients [37; 99]. A lack of intracortical motor inhibition was documented in the motor cortex contralateral to the affected limb [37; 61; 99] and, in some studies, in the ipsilateral motor cortex, although to a lesser extent [61; 99]. The extent of disinhibition was related to pain intensity [99], and immobilisation or disuse has similarly been argued to underlie this [36]. Maihofner et al. [76] suggested that incongruence between changes in cortical and motor sensory representations may contribute to abnormal self perception and body schemas in CRPS. The effectiveness of graded motor imagery and mirror feedback studies in CRPS is based on the reconciliation of motor output and sensory feedback [79-81; 114].

3.3 Psychological factors

There have been some suggestions that CRPS is a manifestation of psychological dysfunction or malingering [112; 113]. Anxiety and depression are relatively common in CRPS [17; 23; 44; 45; 52] and may exacerbate pain [17-19; 40]. However, there is little evidence to suggest that these are the cause, rather than the consequence, of CRPS [16; 23; 26; 52; 70; 78; 92; 110]. For such reasons, psychological dysfunction is generally recognised as secondary to CRPS [59]. It has been suggested that increased systemic levels of noradrenaline and adrenaline in CRPS may be related to psychological distress [53].
Gray matter abnormalities in brain regions responsible for emotional-decision making may underlie observations of cognitive and emotional problems in CRPS [4; 46].

3.4 Conclusions from introductory chapters 1, 2 and 3

CRPS symptoms reflect disturbances both in sensory, autonomic and motor systems which commonly spread outside the affected limb to encompass, in particular, the ipsilateral side of the body. Under normal circumstances pain is transmitted from the periphery to the brain via the dorsal horn of the spinal cord where a number of pain modulatory processes take place. Pain modulatory mechanisms such as DNIC, coeruleospinal and serotonergic pain modulation may be activated in response to a given noxious stimulus, and peripheral and central sensitization may facilitate the transmission of pain. In CRPS, an exaggerated inflammatory response and sympathetic activity may contribute to sensitization of peripheral and central neurons, resulting in cortical changes. A failure of inhibitory pain control could further contribute to this process. However, many speculations still underlie the interaction between these mechanisms. Although cortical changes have been suggested to underlie the hemilateral sensory deficit in CRPS, no research has, to the best of my knowledge, yet attempted to clarify what mechanisms produce these cortical changes and hence contribute to the spread of pain and sensory disturbances in CRPS. As the spread of disturbances is a particularly disabling feature of CRPS, this issue is addressed in this thesis.
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CHAPTER 4

APPROACH

4.1 The studies

To develop an understanding of the mechanisms involved in the hemilateral sensory disturbances of CRPS, it is important to determine whether a standard unilateral painful stimulus in healthy subjects has remote effects that differ between the stimulated and unstimulated sides of the body. The aim of the first series of experiments (Study one) was to investigate the effect of experimental limb pain (cold-induced limb pain) on sensory changes to pressure-pain and sharpness on each side of the forehead in healthy volunteers. In particular, the aim was to establish whether such changes were symmetrical or asymmetrical. Measures of pressure-pain thresholds and sharpness were employed because hemilateral hyperalgesia in CRPS patients was most pronounced to these stimuli in a previous study [8].

In Study one, severe limb pain reduced forehead sensitivity to sharpness and pressure bilaterally with a greater ipsilateral reduction to pressure-pain, indicating the involvement of lateralized and diffuse pain inhibitory control mechanisms. The disruption of such mechanisms could thus be involved in the spread of sensory disturbances in CRPS. This hypothesis was investigated in healthy volunteers in Study two. In a previous study, increased forehead sensitivity to pressure-stimulation with a pointed probe was detected in the most nauseated subjects following optokinetic stimulation possibly due to a disruption of inhibitory pain control [5; 7]. Thus, the effect of optokinetic stimulation and subsequent cold-induced limb pain on sensitivity to pressure-pain and sharpness on each side of the forehead was investigated in healthy volunteers.
As described in chapter 3, exaggerated neurogenic inflammation may contribute to pain in CRPS [1; 2; 11; 15]. The finding of a previous study that unilateral carrageenan-induced hindpaw inflammation in the rat produces thermal hyperalgesia both in the inflamed hindpaw and the non-inflamed forepaw, but not in the contralateral paws [14] prompted us to investigate the possibility of an association between limb inflammation and hemilateral hyperalgesia. Changes in sensitivity to sharpness and pressure-pain on each side of the forehead in healthy volunteers during topical treatment of the forearm with the inflammatory agent, capsaicin, was thus assessed in Study three.

NMDA-receptors are up-regulated in inflamed human skin [13] and probably sensitize primary afferent nociceptors during inflammation and tissue injury [3; 9; 10]. Peripheral NMDA receptors could thus indirectly (by increasing the nociceptive input to the spinal cord thereby inducing central sensitization) contribute to the spread of pain outside the inflamed CRPS limb. In the fourth study, sensitivity to a range of sensory stimuli (touch, pinprick, thermal, pressure, brushing) in the affected limb, unaffected limb, and on each side of the forehead was investigated in patients with CRPS before and after the NMDA antagonist, topical ketamine, was applied to the affected or unaffected limb in a double-blind placebo-controlled trial.

A lack of central inhibitory pain control could also contribute to the sensitization of central neurons in CRPS. A small number of studies in patients with CRPS have suggested that central inhibitory pain control is disrupted [4; 6; 12]. Whether the disruption of such mechanisms is lateralized was investigated in Study five and six. In a previous study, acoustic startle increased pain in the affected limb in the majority of CRPS patients whereas acoustic startle decreased capsaicin-induced thermal hyperalgesia of the forearm in healthy volunteers [4]. Study five assessed whether the CRPS response to startle differed between stimulation in the ear ipsilateral to the affected limb and the ear contralateral to the
affected limb. Similarly, Study six investigated whether noxious cold stimulation of the affected limb versus noxious cold stimulation of the contralateral unaffected limb had differential influences on forehead sensitivity to pressure-pain and sharpness in CRPS patients.

Finally, it is important to determine whether ipsilateral forehead hyperalgesia or hemilateral sensory disturbances occur in pain conditions other than CRPS. Thus Study seven assessed pressure-pain and sharpness sensations on each side of the forehead in chronic non-CRPS pain patients (neuropathic or nociceptive limb pain, back pain or acute herpes zoster/postherpetic neuralgia) and compared these results to those obtained in patients with CRPS.
References


CHAPTER 5

COLD-INDUCED LIMB PAIN DECREASES SENSITIVITY TO PRESSURE-PAIN SENSATIONS IN THE IPSILATERAL FOREHEAD

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Category: Original article

Key words: locus coeruleus; diffuse noxious inhibitory controls; stress-induced analgesia; complex regional pain syndrome; laterality
The aim of this study was to investigate the effect of unilateral limb pain on sensitivity to pain on each side of the forehead. In the first experiment, pressure-pain thresholds and sharpness sensations were assessed on each side of the forehead in 45 healthy volunteers before and after a 10°C cold pressor of the hand and in 18 controls who were not subjected to the cold pressor. In a second experiment, forehead sensitivity was assessed in 32 healthy volunteers before and after a 2°C cold pressor. The assessments were repeated without the cold pressor, and before and after six successive 4°C cold pressor tests. The 10°C cold pressor did not influence forehead sensitivity, whereas the 2°C cold pressor and the 4°C cold pressor tests resulted in bilateral analgesia to sharpness and pressure. The analgesia to pressure was greater in the ipsilateral forehead. Stress-induced analgesia and diffuse noxious inhibitory controls may have contributed to the analgesia to pressure-pain and sharpness sensations bilaterally after the most painful cold pressor tests. The locus coeruleus inhibits ipsilateral nociceptive activity in dorsal horn neurons during limb inflammation, and thus may have mediated the ipsilateral component of analgesia. Pain-evoked changes in forehead sensitivity differed for sharpness and pressure, possibly due to separate thalamic or cortical representations of cutaneous and deep tissue sensibility. These findings suggest that several mechanisms act concurrently to influence pain sensitivity at sites distant from a primary site of painful stimulation.
Introduction

In complex regional pain syndrome (CRPS), pain and sensory disturbances often spread outside the area of initial injury, usually to regions on the ipsilateral side of the body (De Takats, 1937, 1943; Kozin et al., 1976a; Kozin et al., 1976b; Bentley and Hameroff, 1980; Veldman et al., 1993; Veldman and Goris, 1996; Rommel et al., 1999; Maleki et al., 2000; Rommel et al., 2001; Drummond and Finch, 2006). In particular, hyperalgesia is detected in the ipsilateral forehead of most CRPS patients even when no subjective reports of pain or sensory disturbances are reported from this location (Drummond and Finch, 2006).

To fully appreciate such findings, it is important to determine whether a standard unilateral painful stimulus in healthy subjects has effects remote from the painful stimulus that differ between the stimulated and unstimulated sides of the body. Most studies have assessed and reported analgesic effects on the contralateral side of the body in response to cold-induced pain (Willer et al., 1984; Price and McHaffie, 1988; Kakigi, 1994; Witting et al., 1998; Leffler et al., 2002b) and tourniquet-induced ischemic pain (Kosek and Hansson, 1997; Leffler et al., 2002a). To the best of our knowledge, bilateral effects of a standard unilateral painful stimulus have been assessed in healthy subjects in only one study (Tuveson et al., 2006). Analgesia to pressure and heat pain was similar in the left and right thighs after unilateral tourniquet-induced left arm pain in a relatively small sample of 18 participants.

The aim of the present report was to clarify lateralized effects of nociceptive stimulation. We wanted to determine whether a standard unilateral painful stimulus (immersion of the hand in ice-water) would alter pressure-pain or sharp sensations in the
forehead of a large sample of healthy subjects and, if so, to establish whether these changes were symmetrical or asymmetrical.

**Method**

*Subjects*

The sample consisted of male and female university students aged between 17 and 51 years. Participants suffering from medical conditions such as depression, epilepsy, gastric ulcers, ear problems, acute or chronic pain or any other medicated problems were excluded. Some of the subjects participated in both studies. Participants gave their informed consent for the procedures which were approved by the Murdoch University Human Research Ethics Committee.

*Procedures*

Testing was performed in a laboratory maintained at 20 ± 2°C.

**Forehead sensitivity.** To assess the participant’s forehead sensitivity, pain thresholds to firm pressure (PPT) and the degree of sharpness evoked by standard stimuli were measured on each side of the forehead. A spring loaded algometer with a rounded tip (1 cm in diameter) was used to apply pressure at intervals of 80 g to a maximum of 2.3 kg or until the participant felt pain. Sharpness was rated on both sides of the forehead in response to a single application of a firm nylon bristle (Filament 17, Senselab von Frey
Aesthesiometer, Somedic Sales AB, Sweden) on a scale from 0 (not sharp) to 10 (stabbing). Sufficient force was applied to bend the bristle for 1 second.

*Pain in the hand.* The cold pressor (CP) was used to induce pain. The participant placed his or her hand in a cold water bath. The participant was asked to move the hand around in the water to avoid build-up of heat around the hand. The participant rated pain intensity verbally from 0 (no pain) to 10 (extremely severe pain) and also rated the distress associated with the pain in the hand from 0 (none) to 10 (extremely severe distress).

*Experiment 1: Effect of a 10°C cold pressor on forehead sensitivity.* In 45 university students (14 males), forehead sensitivity was assessed before and after participants placed their hand into a cold water bath maintained at 10 ± 1°C for 1 minute. Half of the participants immersed the dominant hand. Participants reported the pain and distress induced by the CP. These measurements were all repeated again 2 minutes later. A control group consisting of 7 male and 11 female students underwent equivalent assessments of the forehead without the CP to control for the effect of repeated forehead assessments.

*Experiment 2: Effect of a 2°C cold pressor and repeated 4°C cold pressors on forehead sensitivity.* Forehead sensitivity was assessed in 32 subjects (13 males) before and after immersing their hand in a 2 ± 1°C cold water bath for 1 minute. The dominant hand was immersed in half of the participants. The assessments were continued at 2 minute intervals for 12 minutes after the CP. Pain and distress ratings associated with the hand immersion were also obtained at these times. To control for effects of repeated forehead assessments, forehead sensitivity was also assessed at equivalent intervals without the CP.
Finally, forehead assessments were conducted before and after six successive 4 ± 1°C CPs each of 1 minute duration at 20 second intervals. Half of the participants immersed their dominant hand. During the 20 second intervals between each CP, participants were asked to rate the pain in the immersed hand and associated distress. The three procedures (a 2°C cold pressor, repeated 4°C cold pressors, and repeated forehead assessments without a cold pressor) were all performed during a single visit. They occurred in random order with sufficient time (median time 15 min, range 10 – 20 min) between them for forehead ratings and pain and distress to return to baseline.

**Statistical analyses.** Student’s *t*-tests were used to assess side differences in forehead sensitivity to pressure and sharpness prior to testing. The degree and asymmetry of forehead sensitivity (ipsilateral versus contralateral) across time and conditions was investigated with analysis of variance for PPT and sharpness ratings. Analysis of variance was also performed for changes in pain intensity and distress across time. Hierarchical linear regression analyses were conducted to assess associations between pain experience (pain intensity, distress), demographics (age, gender) and forehead sensitivity outcome after the CPs, after controlling for forehead sensitivity at baseline. This was done both for general forehead sensitivity and forehead asymmetry to pressure and sharpness. However, the results of these analyses are not reported as they failed to clarify effects of the CP on forehead sensitivity. Finally, differences in pain and distress ratings between the 10°C CP and the 2°C CP were determined using Student’s *t*-tests. Pearson’s correlations assessed any associations between pain and distress ratings and PPT and sharpness ratings in the pooled data from the 10°C CP and the 2°C CP groups. Data are reported as the mean ± standard error of the mean.
Results

Experiment 1: Effect of a 10°C cold pressor on forehead sensitivity

Symmetry of forehead sensations in healthy subjects. Prior to testing, absolute differences in PPTs between the right and left sides of the forehead in the CP group were 80 g or less in the majority of participants (67%) (range 0 - 800 g). No difference was found in 42% of participants. Only 7% (3 participants) had a difference larger than 250 g. PPTs did not differ significantly between the right and left sides [M_right = 675 ± 30 g, M_left = 652 ± 33 g, t(44) = 0.80, not significant]. Absolute differences in sharpness ratings between the right and left sides of the forehead ranged from 0 to 5 prior to testing with the majority (69%) having a difference of 1 or less. No side differences were found in 31% of participants. Sharpness ratings did not differ significantly between the two sides of the forehead [M_right = 3.2 ± 0.2, M_left = 3.3 ± 0.3, t(44) = 0.21, not significant].

In the control group, absolute differences in PPTs between the right and left sides of the forehead were 80 g or less in most participants (89%) (range 0 - 160 g). Fifty percent displayed no difference. Differences in sharpness ratings in this group ranged from 0 to 2 with the majority (89%) reporting a difference of 1 or less. In 56%, no difference in sharpness sensitivity was reported. The right and left sides of the forehead did not differ significantly in response to pressure [M_right = 738 ± 46 g, M_left = 724 ± 47 g, t(16) = 0.90, not significant] or sharpness [M_right = 2.3 ± 0.3, M_left = 2.1 ± 0.3, t(16) = 1.29, not significant].

Change in forehead sensations after the CP. Participants in the CP group experienced moderate pain from the CP (M = 5.3 ± 0.4) which they found mildly
distressing ($M = 2.8 \pm 0.4$). Two minutes after limb immersion, both pain ($M = 0.7 \pm 0.2$) and distress ($M = 0.3 \pm 0.1$) were almost gone.

As shown in Fig. 1, both the CP group and the control group became more sensitive to pressure with each assessment [$p < 0.05$] and no ipsilateral predominance appeared [main effect for Time $F(2,59) = 10.04$, $p < 0.001$]. Sharpness ratings remained unchanged for both groups across forehead assessments (Fig. 2). However, for unknown reasons, the CP group ($M = 3.22 \pm 0.21$) was, in general, more sensitive to sharpness than the control group ($M = 2.24 \pm 0.34$) [main effect for Group $F(1,60) = 6.16$, $p < 0.05$].

Experiment 2: Effect of a 2°C cold pressor and repeated 4°C cold pressors on forehead sensitivity

Symmetry of forehead sensations. Prior to testing, absolute differences in PPTs between the right and left sides of the forehead were again 80 g or less in the majority of participants (91%) (range 0 - 160 g). No difference was found in 53% of participants. PPTs did not differ significantly between the two sides of the forehead [$M_{right} = 726 \pm 33$ g, $M_{left} = 705 \pm 32$ g, $t(30) = 1.86$, not significant]. Absolute differences in sharpness ratings between the right and left sides of the forehead were 1 or less in most participants (91%) (range 0 - 2). No side difference was found in 50% of participants. Sharpness ratings did not differ significantly between the two sides of the forehead [$M_{right} = 2.3 \pm 0.2$, $M_{left} = 2.1 \pm 0.2$, $t(30) = 1.56$, not significant].

Change in forehead sensations after the 2°C CP. As shown in Fig. 3, participants experienced intense pain from the CP which caused them moderate distress. The pain decreased significantly from one assessment to the next [$p < 0.001$] to almost no pain 6
minutes after the CP [main effect for Time F(6,25) = 82.66, p < 0.001]. Distress similarly decreased between consecutive assessments [p < 0.05] and was almost gone 6 minutes after the CP [main effect for Time F(4,27) = 31.35, p < 0.001].

PPTs decreased with the second measurement in the control session [t(30) = 3.91, p < 0.001] whereas PPTs increased significantly after the CP [t(30) = -2.11, p < 0.05] with significantly higher PPTs on the ipsilateral forehead than contralaterally [t(30) = 2.69, p < 0.05] [Condition x Time x Side interaction F(7,24) = 2.79, p < 0.05] (Fig. 4). Sharpness responses decreased gradually after the CP with significant differences to baseline at 6 min [t(30) = 2.97, p < 0.01] and 12 min post CP [t(30) = 2.13, p < 0.05], but remained stable in the control session [Condition x Time interaction F(7,24) = 3.23, p < 0.05]. No side differences in forehead sensitivity were observed for sharpness (Fig. 5).

**Change in forehead sensations after the repeated 4°C CPs.** Participants experienced intense pain from the repeated cold-water immersions (Fig. 6). The initial pain increased with the second immersion [p < 0.05] after which the pain remained relatively stable [main effect for Time F(5,26) = 3.12, p < 0.05]. Participants were moderately distressed about the pain (Fig. 6). Their level of distress did not change with repeated immersions [main effect for Time F(5,26) = 2.48, not significant].

As Fig. 7 illustrates, PPTs increased both ipsilaterally [t(30) = 3.56, p < 0.001] and contralaterally [t(30) = 2.54, p < 0.05] after the CPs with significantly higher PPTs on the ipsilateral forehead than contralaterally [t(30) = 3.66, p < 0.001] [Side x Time interaction F(1,30) = 5.56, p < 0.05]. Sharpness ratings decreased to the same extent on both sides of the forehead [main effect for Time F(1,30) = 8.01, p < 0.01].
Are the differing forehead sensitivity responses from the 10°C CP to the 2°C CP related to pain intensity and distress?

The CP was perceived as significantly more painful by the 2°C CP group (M = 7.7 ± 0.3) than the 10°C CP group (M = 5.3 ± 0.4) \( [t(74) = 4.63, p < 0.001] \). Higher pain ratings were associated with an increase in PPT \( [r = 0.24, p < 0.05] \) and with a decrease in sharpness ratings of the forehead \( [r = -0.28, p < 0.05] \) after the CP. However, pain ratings were unrelated to the development of asymmetry in PPT \( [r = 0.04, \text{not significant}] \) or sharpness \( [r = -0.03, \text{not significant}] \) between the two sides of the forehead from before to after the CP. Distress ratings from the pain were also significantly higher in the 2°C CP group (M = 6.10 ± 0.53) than the 10°C CP group (M = 2.8 ± 0.36) \( [t(74) = 5.35, p < 0.001] \). Higher distress ratings were associated with an increase in PPT \( [r = 0.25, p < 0.05] \) after the CP. However, there was no association with sharpness \( [r = -0.12, \text{not significant}] \).

Discussion

In most CRPS patients, PPTs in the forehead are 250 – 1,500 g lower ipsilateral than contralateral to the affected limb (Drummond and Finch, 2006). In the current experiments, differences in sensitivity between the left and right sides of the forehead in the majority of healthy pain-free participants were small (80 g or less) or non-existent. This also applied for sharpness sensations. It thus appears unusual for healthy individuals to display the asymmetrical forehead sensitivity associated with CRPS.

We investigated whether a unilateral standard painful stimulus in healthy subjects evoked remote effects that differed between the ipsilateral and contralateral sides of the forehead. Inducing moderate limb pain with a 10°C CP did not affect forehead sensitivity.
However, severe limb pain and repeated cold water immersions resulted in bilateral and, particularly, ipsilateral forehead analgesia to pressure. No ipsilateral predominance was seen for the development of analgesia to sharpness. These findings contrast with ipsilateral forehead hyperalgesia in CRPS (Drummond and Finch, 2006), but correspond to some extent with bilateral analgesia during tourniquet-induced ischemic pain in healthy subjects (Tuveson et al., 2006).

During normal pain transmission, signals from nociceptive fibers enter the dorsal horn (Light and Perl, 1979a, 1979b) where they are facilitated or inhibited by pain-modulating mechanisms such as ‘gate control’ (Melzack and Wall, 1965; Basbaum and Fields, 1978), stress-induced hyper- or analgesia (Willer et al., 1981; Quintero et al., 2003), diffuse noxious inhibitory controls (DNIC) (Morton et al., 1987; Villanueva and Le Bars, 1995), or coeruleospinal pain modulation (Proudfit and Clark, 1991; Sluka and Westlund, 1992). In ‘gate control’, inhibitory influences resulting from large-fiber activity (non-noxious input) compete with excitatory influences from small-fiber activity (noxious input) to determine pain perception locally (Basbaum and Fields, 1978). As forehead analgesia developed remotely in the present study, mechanisms other than ‘gate control’ presumably mediated the response.

Acute noxious and non-noxious stress attenuates pain behaviour in animals (Chesher and Chan, 1977; Gamaro et al., 1998) and produces generalized anti-nociception in humans (Willer et al., 1981; Bandura et al., 1988). Such effects are mediated by endogenous opiate and non-opiate mechanisms (Spiaggia et al., 1979; Watkins and Mayer, 1982; Tierney et al., 1991). In the present study, the pain from the 2°C CP and the repeated CPs were perceived as moderately distressing. It is thus likely that stress-induced analgesia contributed to the bilateral forehead analgesia. Indeed, endogenous opioids have been
found to be partly involved in the analgesia following cold water-induced limb pain (Jungkunz et al., 1983; Robertson et al., 2008). In the present study, higher distress ratings were associated with greater forehead analgesia to pressure but not sharpness.

DNIC is also likely to have played a role in the forehead analgesia. The principal feature of DNIC is that painful stimuli diminish or mask pain in a distant part of the body (Villanueva and Le Bars, 1995). In line with the present study, thermal stimuli, particularly noxious cold (Willer et al., 1984; Arendt-Nielsen and Gotliebsen, 1992; Plaghki et al., 1994; Watanabe et al., 1996; Witting et al., 1998; Leffler et al., 2002b; Bouhassira et al., 2003; Lariviere et al., 2007), have been found to activate DNIC in healthy volunteers and inhibit pain elsewhere, as has a range of other stimuli (e.g. mechanical, electrical, ischemic) (Pertovaara et al., 1982; Willer et al., 1984; Price and McHaffie, 1988; Kosek and Hansson, 1997; Bouhassira et al., 2003). Such counter-stimulation appears to inhibit wide dynamic range neurons in the dorsal horn (Le Bars et al., 1979a; Morton et al., 1987) and in the trigeminal nucleus caudalis (Dickenson et al., 1980; Murase and Kawakita, 2000) via a supraspinal loop (Le Bars et al., 1979b; Cadden et al., 1983; Morton et al., 1987). Bilateral DNIC effects, detected by recordings from spinal and trigeminal convergent neurons, have been reported in rat studies involving immersion of paws, tail and muscle in hot water (Bouhassira et al., 1990; Bouhassira et al., 1992). DNIC also appears to act bilaterally in response to noxious conditioning stimuli in humans (Tuveson et al., 2006). Thus, the severe and prolonged limb immersions in the present study probably activated DNIC as well as stress-induced analgesia, resulting in bilateral forehead analgesia to pressure and sharpness.

In line with previous studies which found that the intensity of the stimulus is associated with the strength of the resultant DNIC (Willer et al., 1984; Villanueva and Le Bars, 1985; Fujii et al., 2006), the 10°C CP apparently did not activate DNIC. Whether the
amount of nociceptive discharge or perceived pain determines the extent of DNIC, or
whether pain is even necessary for the induction of DNIC, is controversial (Lautenbacher et
al., 2002; Le Bars, 2002; Baad-Hansen et al., 2005; Pud et al., 2005; Granot et al., 2008). In
the present experiments, higher limb pain ratings were associated with a greater reduction
in sensitivity to forehead pressure and sharpness.

The analgesic response to pressure was greater in the ipsilateral forehead. The
mechanism of this effect is unclear, but may have involved coeruleospinal pain modulation.
The nucleus locus coeruleus (LC), located in the dorsolateral pons, induces anti-nociception
when stimulated electrically or chemically (Margalit and Segal, 1979; Jones and Gebhart,
1986a; West et al., 1993). Activation of the LC is thought to inhibit nociceptive activity in
dorsal horn (Jones and Gebhart, 1986b) and trigeminal subnucleus caudalis neurons
(Tsuruoka et al., 2003c) via noradrenergic projections (Westlund et al., 1983; Fritschy and
Grzanna, 1990) that act on $\alpha_2$-adrenoceptors (Jones and Gebhart, 1986a, 1986b). Although
the LC projects bilaterally to the dorsal horn (Clark et al., 1991; Clark and Proudfit, 1992;
Sluka and Westlund, 1992), activity in LC projections increases in the ipsilateral dorsal
horn but not contralaterally during unilateral hindpaw inflammation (Tsuruoka and Willis,
1996a, 1996b; Tsuruoka et al., 1999; Tsuruoka et al., 2003b). The finding of a bilateral
increase in Fos expression in the LC during unilateral hindpaw inflammation suggests that
the ipsilateral activation emanates bilaterally, but perhaps travels through the dorsolateral
funiculus ipsilaterally (Tsuruoka et al., 2003a). This is still a contentious issue, however.

Importantly, the LC appears to project to all segmental levels of the spinal cord.
Injection of anterograde transport of Phaseolus vulgaris leucoagglutinin (PHA-L) in the LC
resulted in consistent labeling in cervical, thoracic and lumbar segments of the spinal cord
(Proudfit and Clark, 1991). Consistent with this, Tsuruoka et al. (2004) measured the
thermal response threshold on all four paws of the rat during unilateral hindpaw inflammation and found shorter paw withdrawal latencies for the inflamed hindpaw in rats with bilateral LC lesions than in sham operated rats. This was also observed in the non-inflamed, but hyperalgesic, ipsilateral forepaw but not in the contralateral hind- or forepaw. Such studies suggest that the coeruleospinal modulation system plays a role in suppressing inflammation-induced hyperexcitability of nociceptive dorsal horn neurons that extend through the propriospinal pathways, although it may not completely deter such activity. Importantly, electrical stimulation of primary afferent A-delta fibers produces excitation of descending noradrenergic neurons from the LC, resulting in an increase in the level of noradrenaline in the dorsal horn (Hitoto et al., 1998). The increase was seen ipsilaterally but not contralaterally after carageenan inflammation of the hindpaw (Tsuruoka et al., 1999). It is thus likely that the finding of ipsilateral analgesia in the present study reflects ipsilateral coeruleospinal pain modulation, perhaps acting in concert with stress-induced analgesia and DNIC. Pain intensity did not appear to be the determining factor for this component of the analgesia as we failed to find any association between pain ratings and forehead asymmetry.

Interestingly, the ipsilateral analgesia occurred for pressure but not sharpness. Dissociations between such sensations were also found in patients with central post-stroke pain (Mailis and Bennett, 2002) and in CRPS patients (Drummond and Finch, 2006) who often display a loss of cutaneous sensation but a persistence or increase in deep-pressure pain. Pressure also induces pain more so than cutaneous stimulation in patients with thalamic lesions (Riddoch, 1938). These findings suggest that different central mechanisms account for painful cutaneous versus deep-pressure sensations. Consistent with this, cutaneous nociceptors appear to project predominantly to lamina I and II of the dorsal horn.
whereas muscle afferents innervate laminae I and V (Craig et al., 1988; Mense and Craig, 1988; Ohtori et al., 2000). Furthermore, pain of superficial origin evokes neural activity in different brain sites than pain of deeper origin (Henderson et al., 2006).

Some limitations apply to this study as it was performed in a predominantly young, educated, female population. Nonetheless, women were studied across every stage of the menstrual cycle rendering this an unlikely influence, and gender and age were unrelated to the development of analgesia. The present findings demonstrate that limb pain in healthy participants induces bilateral analgesia to mechanical stimulation and ipsilateral analgesia to pressure in the forehead, suggesting the involvement of stress-induced analgesia, DNIC and perhaps ipsilateral coeruleospinal pain-controlling mechanisms. Thus, disruption of these mechanisms may contribute to ipsilateral forehead hyperalgesia in CRPS.


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Fig. 1. PPT for sides of the forehead ipsilateral and contralateral to the CP in the CP group and equivalent sides of the forehead in the control group. PPTs decreased significantly in both groups after the CP. Error bars represent standard errors and the arrow represents the CP in the CP group.
Fig. 2. Sharpness ratings for sides of the forehead ipsilateral and contralateral to the CP in the CP group and equivalent sides of the forehead in the control group. Sharpness ratings were unchanged across measurements for both groups. The CP group was significantly more sensitive to sharpness than the control group. Error bars represent standard errors and the arrow represents the CP in the CP group.
Fig. 3. Hand pain and distress ratings for 12 minutes after the 2 °C. Error bars represent standard errors and the arrow represents the CP.
Fig. 4. PPT before and for 12 minutes after the 2 °C CP and equivalent time intervals in the control session for sides of the forehead ipsilateral and contralateral to the immersed hand. PPTs decreased with the second measurement in the control session, but increased significantly after the CP (* p < 0.05). PPTs after the CP were significantly greater ipsilaterally than contralaterally (* p < 0.05). Error bars indicate standard errors and the arrow represents the CP in the CP condition.
Fig. 5. Sharpness ratings before and for 12 minutes after the 2 °C CP and equivalent time intervals in the control session for sides of the forehead ipsilateral and contralateral to the immersed hand. Sharpness ratings were unchanged in the control session, but had decreased significantly 6 min and 12 min after the CP. Error bars indicate standard errors and the arrow represents the CP in the CP condition.
Fig. 6. Hand pain and distress ratings after each 4 °C immersion. Error bars represent standard errors.
Fig. 7. PPT and sharpness ratings before and after the repeated CPs for sides of the forehead ipsilateral and contralateral to the immersed hand. Sensitivity to pressure and sharpness decreased bilaterally. PPTs were greater ipsilaterally than contralaterally after the CPs (**) \( p < 0.01 \). Error bars indicate standard errors and the arrow represents the repeated CPs.
CHAPTER 6
EFFECT OF LIMB PAIN AND MOTION SICKNESS ON
SCALP TENDERNESS

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Pages: 29
Tables: 2
Figures: 4

Key words: diffuse noxious inhibitory controls, stress-induced analgesia, cold pressor, motion sickness, complex regional pain syndrome, hyperalgesia
Abstract

A disruption of central pain control may be involved in the development of scalp tenderness during motion sickness. The aim of this study was to investigate the effect of limb pain on sensitivity to noxious stimulation on each side of the forehead during motion sickness. Eighty-five healthy volunteers were subjected to a cold pressor task of the hand on two occasions. On one of these occasions, the cold pressor was preceded by optokinetic stimulation to induce symptoms of motions sickness. Pressure-pain thresholds and ratings of sharpness to a firm bristle were obtained from each side of the forehead before and after each stimulus. On its own, the CP decreased forehead sensitivity to sharpness and opposed an increase in sensitivity to pressure-pain in pain sensitive individuals, suggesting involvement of diffuse noxious inhibitory controls (DNIC) and stress-induced analgesia (SIA). During residual motion sickness, forehead sensitivity to pressure and sharpness increased, but decreased following the CP. These findings suggest that DNIC and SIA remained intact during residual motion sickness. Forehead sensitivity to sharpness and pressure varied independently, possibly due to the recruitment of separate central deep versus cutaneous tissue sensibility pathways.
Introduction

In complex regional pain syndrome (CRPS), pain and sensory disturbances may spread from the painful limb to other areas of the body [33; 43; 44]. Both sides of the body may be affected [20; 48], but most marked is a spread of sensitivity ipsilaterally [15]. Drummond and Finch [15] found that sensitivity to sharpness from a firm bristle in the affected limb of most CRPS patients was associated with similar sensations in the ipsilateral forehead, and that pressure-pain thresholds were between 250 g to 1,500 g lower in the ipsilateral forehead than contralaterally, consistent with an ipsilateral spread of hyperalgesia. Whether this spread is a specific pathological sign of CRPS, as the investigators speculated, is unknown. If so, it may provide for a possible diagnostic tool.

We recently investigated whether a standard unilateral painful stimulus in healthy subjects has effects remote from the site of stimulation that mimic the pattern seen in CRPS [25]. While a 10°C cold water immersion had no effect on forehead sensitivity, a single 2°C immersion and six repeated 4°C immersions resulted in bilateral analgesia in the forehead both for sharpness ratings to a firm bristle and pressure-pain thresholds. In addition, analgesia to pressure-pain was greater ipsilaterally than contralaterally. These findings contrast with the ipsilateral forehead hyperalgesia in CRPS. In fact, such findings suggest that diffuse noxious inhibitory controls (DNIC), acting on wide dynamic range neurons in the dorsal horn upon nociceptive stimulation [55], inhibited sensitivity in the forehead, perhaps in concert with stress-induced analgesia (SIA) [46; 49; 57] and coeruleospinal pain modulation [50-54]. In the latter mechanism, noradrenergic projections from the locus coeruleus act on α2- adrenoceptors proximally as well as distally in the ipsilateral dorsal
horn during unilateral limb inflammation, and could thus account for ipsilateral forehead analgesia during intensely painful cold pressor tests.

Interestingly, central pain control mechanisms such as DNIC and SIA seem to be disrupted in CRPS as painful forehead cooling and startle with a loud tone increase rather than reduce limb pain [10; 13]. Recently Seifert et al.[45] reported a slower decline in pain ratings during repetitive noxious electrical stimulation of both the affected and unaffected limb in CRPS patients compared to controls consistent with reduced inhibitory pain control. Perhaps it is a lack of such pain modulation which accounts for the spread of pain in CRPS.

The present experiment investigated whether limb pain accentuates scalp tenderness associated with residual motion sickness induced by optokinetic stimulation (OKS) in healthy people. OKS has been shown to induce mechanical hyperalgesia in the forehead of nauseated subjects [11], leading to speculation that activation of certain brainstem nuclei during motion sickness disrupts pain inhibitory mechanisms such as DNIC or SIA [14]. If this provides an adequate model for mimicking the lack of central pain control in CRPS patients, and if this lack of control is responsible for the ipsilateral forehead hyperalgesia, cold-induced pain in the hand should aggravate mechanical hyperalgesia in the ipsilateral forehead during residual motion sickness.

Materials and Methods

Subjects

Participants were 85 young and mature age university students (26 males) ranging in age from 17 to 59 years (median age 22). Participants with psychiatric problems or medical problems including acute or chronic pain or vestibular problems were excluded, as were medicated participants. The study was approved by the Murdoch University Human
Research Ethics Committee. Participants gave their informed consent to participate; they were informed that they might experience motion sickness from optokinetic stimulation and pain from the cold pressor, but they were not otherwise aware of the specific purpose or expected findings of the study.

Procedures

Forehead sensitivity. A spring loaded algometer with a rounded tip (1 cm in diameter) was used to assess pressure-pain thresholds (PPT) on each side of the forehead. Pressure was applied at intervals of 80 g to a maximum of 2.3 kg or until the participant reported pain [25]. Sharpness was rated in response to a single application of a firm nylon bristle (Filament 17, Senselab von Frey Aesthesiometer, Somedic Sales AB, Sweden) on each side of the forehead on a scale from 0 (not sharp) to 10 (stabbing). Enough force was applied to bend the bristle for 1 s [25].

Pain in the hand. The cold pressor (CP) was used to induce pain. The participant immersed his or her hand in a cold water bath maintained at 10 ± 1 °C for 1 min [25]. The dominant hand was immersed in half of the participants and the non-dominant hand in the other half. The participant moved the hand around in the water to avoid build-up of heat around the hand. Pain intensity was rated verbally from 0 (no pain) to 10 (extremely severe pain) and distress associated with the pain in the hand was rated from 0 (none) to 10 (extremely severe).

Optokinetic stimulation. To induce symptoms of motion sickness, the participant sat on a stationary chair with his or her head and shoulders inside an illuminated drum 50 cm in diameter, 70 cm in height and painted internally with 24 pairs of vertical black and white
stripes each 3.3 cm wide [11]. The drum revolved 10 times per minute for 10 min or until participants could no longer tolerate the sensations evoked by optokinetic stimulation. To enhance the illusion of movement, the participant was asked to look at a distant point rather than watch the stripes move past. The mismatch between the visual illusion of movement and contrasting vestibular and proprioceptive cues induced motion sickness. Symptoms of motion sickness (dizziness, nausea and headache) were rated by the participant from 0 (none) to 10 (extremely severe).

**Trial sequence.** Sessions took place in a laboratory maintained at 20 ± 2 ºC. Sensitivity to mechanical stimulation on each side of the forehead and motion sickness symptoms were assessed both before and after OKS. The participant then placed his or her hand into the cold water for 1 min. Straight after removing the hand and 2 min later, the participant reported the pain and distress associated with the hand immersion along with motion sickness symptoms, and forehead sensitivity assessments were repeated. During a separate session randomly performed at least 3 days (median 7 days, range 3-8) prior to or after the OKS session, the cold pressor and associated assessments were repeated without OKS (henceforth termed the “isolated” cold pressor).

**Statistical analyses.** Student’s t-tests were used to assess side differences in forehead sensitivity to pressure and sharpness prior to testing. Changes in dizziness, nausea and headache to OKS (before OKS, after OKS, after the CP, 2 min after the CP) were investigated with analyses of variance as were changes in pain and distress to the CP (after the CP, 2 min after the CP) in the residual motion sickness versus no motion sickness conditions. The Huynh-Feldt epsilon was used to correct for violations of sphericity. Analyses of variance were also used to assess changes in the degree and asymmetry of
forehead sensitivity (ipsilateral versus contralateral) to sharp and pressure sensations from before OKS to after OKS as well as to assess changes in forehead sensitivity from before the CP to after and 2 min after the CP in the two conditions (with and without residual motion sickness). Planned comparisons, analyses of variance or student’s $t$-tests were used as appropriate to explore significant findings. Pearson’s correlations assessed associations between changes in forehead sensitivity to pressure and sharpness and motion sickness symptoms. Data are reported as the mean ± standard error of the mean.

**Results**

*Symmetry of forehead sensations in healthy subjects*

Prior to testing, the majority of participants displayed absolute PPT differences between the right and left sides of the forehead of 80 g or less (69%) (range 0 - 800 g). There was no difference in 34% of participants. Eight participants (9%) had a difference larger than 250 g (i.e. at a level similar to that of the majority of CRPS patients). Overall, forehead sensitivity to pressure-pain did not differ significantly between the right and left sides [$M_{\text{right}} = 710.35 \pm 23.60$ g, $M_{\text{left}} = 698.12 \pm 25.23$ g, $t(84) = 0.63$, not significant]. Sharpness ratings also did not differ significantly between the two forehead sides prior to testing [$M_{\text{right}} = 3.03 \pm 0.17$, $M_{\text{left}} = 3.04 \pm 0.19$, $t(84) = 0.09$, not significant]. The absolute difference in sharpness ratings between the sides of the forehead was a rating of 1 or less in the majority of participants (81%) (range 0 - 5). Sharpness was identical on both sides of the forehead in 45% of the participants.
Development of motion sickness after OKS

Eleven participants asked for the drum to be stopped during rotation [mean time for this group = 5.18 ± 0.61 min]. The other 74 participants stayed in the drum for the entire 10 minute period. Participants reported the development of dizziness, nausea and headache after OKS [p < 0.001 for all symptoms]. The symptoms decreased after immersion of the hand in the water [p < 0.001 for all symptoms] and decreased further 2 minutes later [p < 0.001 for dizziness and nausea and p < 0.01 for headache] (Fig. 1) [main effect for Time for dizziness F(2.22,186.75) = 197.02, p < 0.001, nausea F(2.05,171.94) = 104.48, p < 0.001) and headache F(2.25,189.12) = 31.24, p < 0.001]. Two minutes after the CP, the symptoms were still slightly higher than at baseline [p < 0.01 for dizziness, p < 0.001 for nausea and headache].

Pain and Distress

Participants, in general, experienced moderate pain from the isolated CP (M = 5.21 ± 0.28). They found it mildly distressing (M = 2.59 ± 0.25). However, while some participants perceived no or very little pain from the CP, others reported much more severe pain. As pain is generally considered important for DNIC and was previously associated with the degree of forehead analgesia following a CP task [25], we allocated participants to two groups based on their pain score during the isolated CP: those with a mean pain score of 3 or less (M = 1.83 ± 0.26, range 0 - 3) who were regarded as pain insensitive (n = 23) and those with a pain score of more than 3 (M = 6.46 ± 0.21, range 3.5 - 10) (pain sensitive, n = 62). Sex, age, and mean PPT before testing were similar in the two groups (Table 1). However, the pain sensitive group reported greater sharpness sensations in the forehead prior to the experiment than the pain insensitive group [main effect for Group F(1.83) =
5.94, p < 0.05. The length of time spent in the drum and intensity of motion sickness induced by OKS were similar in the two groups.

The CP (during and without residual motion sickness) consistently induced more pain in the pain sensitive than the pain insensitive group [main effect for Group F(1,83) = 88.05, p < 0.001] (Fig. 2). The pain induced by the CP virtually resolved in both groups 2 min after the CP regardless of whether it was preceded by OKS [main effect for Time F(1,83) = 362.40, p < 0.001]. This decrease was greater in the pain sensitive group than the pain insensitive group [t(83) = 9.09, p < 0.001] [Time x Group interaction F(1,83) = 82.66, p< 0.001] possibly because the CPs induced more pain in this group in the first place.

Interestingly, the pain sensitive group reported a similar amount of pain from the CP in the presence or absence of residual motion sickness [t(61) = 0.59, not significant] whereas motion sickness increased cold-induced pain in the pain insensitive group [t(22) = 3.18, p < 0.01] [Condition x Time x Group interaction F(1,83) = 5.51, p < 0.05] (Fig. 2).

The CP tests also produced consistently more distress in the pain sensitive than the pain insensitive group irrespective of residual motion sickness [main effect for Group F(1,83) = 29.70, p < 0.001] (Fig. 2). Distress induced by the CP decreased in both groups 2 min after the CP both in the presence and absence of residual motion sickness [main effect for Time F(1,83) = 86.00, p < 0.001]. As with pain, the decrease in distress was greater in the pain sensitive than the pain insensitive group [t(83) = 5.55, p < 0.001] [Time x Group interaction F(1,83) = 30.81, p < 0.001] probably because distress initially was greater in this group.

Scalp tenderness after OKS

Forehead sensitivity to pressure-pain increased after OKS [main effect for Time F(1,84) = 47.34, p < 0.001] (Fig. 3). This occurred in both pain groups alike and to a
similar extent on both sides of the forehead. This was also the case for sharpness [main effect for Time F(1,84) = 31.79, p < 0.001] (Fig. 4). Again the response did not differ between the two sides of the forehead or between the pain groups.

The development of scalp tenderness to pressure-pain and sharpness was associated with nausea (Table 2). In addition, the development of scalp tenderness to pressure-pain was associated with the development of dizziness, and scalp tenderness to sharpness was associated with headache.

Changes in forehead sensations after the CP during and without residual motion sickness

Changes in forehead sensitivity to pressure-pain after the CP tests are shown in Figure 3. A significant condition by time by group interaction emerged for PPTs [F(2,166) = 3.17, p < 0.05]. Post hoc analyses of variance revealed that the pain insensitive group became more sensitive to pressure-pain immediately after the isolated CP [p < 0.001] [main effect for Time (before, after and 2 min after the CP) F(2,44) = 5.74, p < 0.01]. In the pain sensitive group, this increase in sensitivity did not occur until 2 min after the isolated CP [p < 0.05] [main effect for Time (before, after and 2 min after the CP) F(2,122) = 3.52, p < 0.05]. In contrast, during residual motion sickness, both groups became less sensitive to pressure-pain immediately after the CP [main effect for Time in the pain insensitive group (before and after the CP) F(1,22) = 3.65, p = 0.07] [main effect for Time in the pain sensitive group (before and after the CP) F(1,61) = 4.22, p < 0.05]. Participants were, in general, more sensitive to pressure-pain during residual motion sickness (M = 596.36 ± 18.29) than during CP stimulation alone (M = 653.74 ± 22.91) [main effect for Condition F(1,83) = 14.34, p < 0.001].

As shown in Figure 4, ratings of forehead sharpness also differed between the two pain groups across the time course of the experiment [Condition x Time x Group
interaction, F(2,166) = 4.33, p < 0.05]. In post hoc analyses of variance, ratings of sharpness remained unchanged in the pain insensitive group [main effect for Time (before, after and 2 min after the CP) F(2,44) = 1.40, not significant] whereas sharpness ratings decreased significantly in the pain sensitive group 2 min after the isolated CP [p < 0.01] [main effect for Time (before, after and 2 min after the CP) F(2,122) = 4.84, p < 0.01].

During residual motion sickness, forehead sensitivity to sharpness decreased immediately after the CP in the pain sensitive group [p < 0.001], followed by a further decrease 2 min later [p < 0.01] [main effect for Time (before, after and 2 min after the CP) F(2,122) = 21.13, p < 0.001]. A decrease was also reported by the pain insensitive group albeit not until 2 min after the CP [p < 0.001] [main effect for Time (before, after and 2 min after the CP) F(2,44) = 10.84, p < 0.001]. No side differences to sharpness emerged at any time in either group or condition.

**Discussion**

This study confirmed previous observations that healthy people generally show little difference in sensitivity between the two sides of the forehead to pressure or sharpness [25]. In contrast, the majority of CRPS patients display ipsilateral forehead hyperalgesia [15]. Nonetheless, 9% of participants displayed differences to a similar extent as CRPS patients.

As central pain control appears to be disrupted in CRPS [10; 45], we wanted to assess whether disrupting pain control in healthy volunteers during residual motion sickness would result in a spread of sensitivity from a standard painful stimulus to the ipsilateral forehead. Scalp tenderness developed during residual motion sickness. Nevertheless, limb pain produced by cold water immersion did not induce ipsilateral
forehead hyperalgesia. Instead, bilateral forehead analgesia both to pressure-pain and sharpness emerged after the CP, in particular in subjects who reported moderate to severe pain from the hand immersion.

Remote analgesia to limb pain during residual motion sickness: evidence of diffuse noxious inhibitory controls (DNIC) and stress-induced analgesia (SIA)

DNIC operates on the counter-irritation principle whereby one noxious stimulus inhibits another irrespective of body location [55]. The neurons that mediate DNIC originate in the subnucleus reticularis dorsalis of the caudal medulla [3] and inhibit wide dynamic range neurons in the trigeminal nucleus caudalis [8; 36] and dorsal horn [29; 35] via a supraspinal loop [28]. The DNIC effect has been reported following various conditioning stimuli (e.g. mechanical, electrical, ischemic) [4; 26; 38; 40; 59], in particular noxious cold [1; 4; 27; 30; 39; 56; 59; 61].

The isolated CP may have activated DNIC, albeit weakly, in subjects who found the CP moderately or intensely painful. In participants who found the CP only mildly painful or not at all painful, forehead responses were similar to those during repeated forehead assessments (i.e., immediately decreased PPTs and unchanged sharpness sensations) [25]. In contrast, the isolated CP decreased forehead sensitivity to sharpness and inhibited an immediate decrease in PPT in pain sensitive participants. As the pain sensitive group also experienced significantly greater distress from the CP than the pain insensitive group, SIA [2; 5; 17; 58] may have added to this inhibitory forehead response. Short term stress appears to activate non-opioid analgesia whereas longer term stress activates opioid analgesia [9; 31]. As the CP test lasted only 1 min, analgesia was probably mediated by a non-opioid mechanism in the present case.
Contrary to expectations, the pain modulatory mechanisms of DNIC and SIA appeared to remain intact during residual motion sickness. The inhibitory response in the pain sensitive group was stronger, not weaker, during residual motion sickness in that forehead sensitivity both to pressure-pain and sharpness decreased immediately after the CP. The inhibitory effect probably was stronger during residual motion sickness than the CP alone because it was associated with a concurrent return of forehead sensitivity to baseline (after an increase following OKS) as motion sickness resolved.

The isolated CP failed to inhibit pain sensitivity in the forehead in the group who perceived no or very little pain from the CP. This lack of inhibition was unrelated to age, gender or forehead sensitivity to pressure-pain prior to the study as these were similar in the two groups. However, sharpness ratings were lower in the pain insensitive group prior to testing, suggesting a higher degree of general pain tolerance in this group. Biological differences or better coping skills in pain insensitive than pain sensitive people may account for this difference [7; 18; 21]. Interestingly, the central release of endogenous opioids during cold water limb immersions was greater in pain insensitive individuals than pain sensitive individuals [42]. Perhaps such characteristics prevented the development of pain and distress from reaching a level sufficient to activate DNIC or SIA.

*Greater limb pain during residual motion sickness: disruption of tonic opioid release?*

Curiously, the pain insensitive group reported greater pain from the cold pressor during residual motion sickness than without. There is some evidence to support the existence of a tonically active opioid system in healthy individuals [16; 24]. For example, during sustained sadness, opioid activity decreases in the rostral anterior cingulate region in non-depressed controls [24]. It is tempting to speculate that motion sickness disrupted this system in pain-insensitive participants. Future research is needed to confirm this.
Residual motion sickness and scalp tenderness

Motion sickness results from a sensory mismatch between visual, vestibular and proprioceptive inputs [47]. During OKS, the mismatch between sitting still versus the perception of movement results in symptoms characteristic of motion sickness i.e. dizziness, nausea and headache [11; 22]. In the present study, OKS was employed to induce symptoms of motion sickness because this was found previously to increase forehead sensitivity to pressure applied with a pointed probe, at least in nauseated subjects [11]. The present study confirmed such findings of scalp tenderness both to blunt pressure and sharpness in association with symptoms of motion sickness. Consistent with previous findings, nausea was the symptom most consistently associated with the development of scalp tenderness. In addition, headache was weakly related to the development of scalp tenderness to sharpness, and dizziness to the development of scalp tenderness to pressure-pain. Dizziness, nausea and headache are also characteristic of migraine [12], implying that scalp tenderness develops in conjunction with or in response to symptoms of migraine. Interestingly, susceptibility to motion sickness is greater than normal in migraine sufferers [23], and nausea is more likely to develop in response to OKS in migraine sufferers than controls [11].

Drummond [14] speculated that failure of an inhibitory mechanism to suppress symptoms such as dizziness, nausea and headache increases vulnerability both to motion sickness and migraine. In the present study, DNIC and, perhaps non-opiate SIA, appeared to remain functional during residual motion sickness. The increase in cold-induced pain during residual motion sickness in the pain insensitive group suggests that motion sickness may instead be associated with disruption of a tonically active opioid system [16; 42] or with a direct increase in the excitability of central nociceptive circuits.
Dissociation between pressure and sharpness

Sensitivity to pressure-pain and sharpness varied independently in the current study. Similar dissociation was observed previously to noxious cold water limb immersion in healthy subjects [25]. These sensations are also dissociated in CRPS [15] and in patients with thalamic lesions or central post-stroke pain [32; 41], who often display a loss of cutaneous sensation but a persistence or hypersensitivity to deep-pressure. Separate sensory pathways may thus be responsible for cutaneous versus deep-pressure sensations. Evidence that cutaneous nociceptors predominantly innervate laminae I and II of the dorsal horn [60] whereas nociceptors from deeper tissues project to laminae I and V [6; 34; 37] is consistent with this idea. Furthermore, superficial pain induces neural activity in different brain regions than pain of deeper origin [19].

Limitations and conclusion

Some limitations apply to the present study as it was performed during residual motion sickness, due to the impracticality of conducting forehead assessments during drum rotation. Replicating the study using other means of motion sickness induction, to allow for concurrent forehead assessments, may clarify any differences between peak and residual motion sickness. Nonetheless, this study confirmed previous findings of scalp tenderness both to pressure and sharpness during residual motion sickness. The mechanism underlying this hyperalgesia did not appear to involve disruption of DNIC or SIA. Cold water limb immersion failed to produce ipsilateral forehead hyperalgesia during residual motion sickness and can thus be ruled out as an appropriate model for the spread of ipsilateral hyperalgesia in CRPS.
References


Table 1

Sex, age, mean PPT and mean sharpness ratings before testing, time in the drum and motion sickness symptoms in the pain insensitive and pain sensitive groups

<table>
<thead>
<tr>
<th></th>
<th>Pain Insensitive</th>
<th>Pain Sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n)</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Females (n)</td>
<td>17</td>
<td>42</td>
</tr>
<tr>
<td>Age (years) ± SEM</td>
<td>24.39 ± 1.49</td>
<td>24.61 ± 1.09</td>
</tr>
<tr>
<td>PPT (g)</td>
<td>738.26 ± 43.19</td>
<td>691.61 ± 26.30</td>
</tr>
<tr>
<td>Sharpness (0 – 10)*</td>
<td>2.37 ± 0.32</td>
<td>3.28 ± 0.20</td>
</tr>
<tr>
<td>Time in drum (min)</td>
<td>9.40 ± 0.34</td>
<td>9.37 ± 0.23</td>
</tr>
<tr>
<td>Dizziness (0-10)</td>
<td>4.37 ± 0.55</td>
<td>5.26 ± 0.26</td>
</tr>
<tr>
<td>Nausea (0-10)</td>
<td>3.35 ± 0.57</td>
<td>4.65 ± 0.37</td>
</tr>
<tr>
<td>Headache (0-10)</td>
<td>1.65 ± 0.42</td>
<td>2.23 ± 0.30</td>
</tr>
</tbody>
</table>

Sharpness was greater in the pain sensitive than pain insensitive group (* p < 0.05). No differences between the left and right sides of the forehead existed in either group.
Table 2

Pearson’s correlations between changes in forehead sensitivity after OKS and the development of motion sickness

<table>
<thead>
<tr>
<th>Change in mean forehead sensitivity after OKS</th>
<th>Change in motion sickness symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dizziness</td>
</tr>
<tr>
<td>PPT</td>
<td>-0.23*</td>
</tr>
<tr>
<td>Sharpness</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01
Fig. 1. Motion sickness symptoms before and after OKS and the subsequent CP. All symptoms increased significantly after OKS (*** p < 0.001 all symptoms), followed by a significant decrease in severity immediately after the CP (*** p < 0.001 all symptoms). Error bars indicate standard errors.
Fig. 2. Hand pain and distress ratings in the pain insensitive and the pain sensitive groups for 2 minutes after the CP during residual motion sickness and without. The pain insensitive group experienced more pain from the CP during residual motion sickness than without OKS (* p < 0.01) whereas no difference was detected in the pain sensitive group. Pain and distress had almost disappeared 2 minutes after the CP in both groups irrespective of motion sickness. Error bars represent standard errors.
Fig. 3. PPTs at times before and after the CP during and without residual motion sickness for the pain insensitive and pain sensitive groups.

PPTs decreased in the pain insensitive group after the isolated CP (**p < 0.001). This decrease was delayed in the pain sensitive group until 2 minutes after the CP (*p < 0.05). After OKS, PPTs decreased in both groups (**p < 0.001). However, when the CP was subsequently induced, PPTs increased bilaterally (# p = 0.07; * p < 0.05). Errors bars represent standard errors.
Fig. 4. Sharpness ratings at times before and after the CP during and without residual motion sickness for the pain insensitive and pain sensitive groups. Sensitivity to sharpness decreased 2 min after the isolated CP in the pain sensitive group (\(\star\star\star\ p < 0.001\)) but no change was seen in the pain insensitive group. After the OKS, sharpness ratings increased in both groups (\(\star\star\star\ p < 0.001\)), but decreased immediately after the CP in the pain sensitive group (\(\star\star\star\ p < 0.001\)) with a further decrease 2 min later (\(\star\star\ p < 0.01\)). During residual motion sickness, the CP induced a reduction in sharpness ratings in the forehead in the pain insensitive group 2 min after the CP (\(\star\star\star\ p < 0.001\)). Error bars represent standard errors.
CHAPTER 7

LIMB INFLAMMATION PRODUCES ANALGESIA TO
PRESSURE-PAIN IN THE IPSILATERAL FOREHEAD OF
HEALTHY VOLUNTEERS

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Key words: diffuse noxious inhibitory controls; stress-induced analgesia; capsaicin; locus coeruleus; hyperalgesia
Abstract

This study aimed to investigate the remote effects of topical capsaicin, an inflammatory agent, applied to the forearm on pain sensitivity in each side of the forehead in 17 healthy volunteers. Pressure-pain thresholds and sharpness sensations were assessed on each side of the forehead before and during 48 hours of capsaicin treatment. Heat was applied to the treated area to rekindle pain at times of assessment. Tests of sensation were also performed in the treated forearm and the contralateral forearm before and after 48 hours of treatment. Hyperalgesia to sharpness, but not pressure-pain, developed in the treated area whereas sensations remained stable in the contralateral forearm. Sharpness ratings decreased bilaterally in the forehead 6 hours after treatment, and an ipsilateral analgesia to pressure-pain developed when the treated area was heated after 48 hours of treatment. No contralateral changes were observed for pressure-pain. Diffuse noxious inhibitory controls and stress-induced analgesia may account for the bilateral decrease in forehead analgesia to sharpness, whereas the ipsilateral forehead analgesia to pressure-pain may arise due to activation of coeruleospinal pain control. These findings suggest that pain modulation involves unilaterally extending mechanisms in addition to local and generalized controls. The dissociated changes to sharpness and pressure-pain indicate distinct cutaneous and deep central pain pathways.
Introduction

The present understanding of the perception of pain is that it is the end result of a number of inhibitory and facilitatory influences on nociceptive neurotransmission in the central nervous system. Some well-known mechanisms that may be activated in response to a painful stimulus are the gate-control response (Melzack and Wall, 1965; Basbaum and Fields, 1978), diffuse noxious inhibitory controls (Morton et al., 1987; Villanueva and Le Bars, 1995), stress-induced analgesia (Willer et al., 1981) and stress-induced hyperalgesia (Quintero et al., 2003). Also the locus coeruleus (LC) nuclei have been implicated in descending inhibitory control (Jones, 1991; Zhang et al., 1997). Apart from the gate-control effect which is concerned with pain perception locally, the remaining mechanisms are generally thought to exert widespread inhibitory or facilitatory influences.

Findings are now beginning to emerge to challenge this concept of widespread inhibition and facilitation. In rats, unilateral carageenan inflammation of the hindpaw induced hyperalgesia, not just in the injected hindpaw, but also in the ipsilateral non-inflamed forepaw four hours after the carageenan injection (Tsuruoka et al., 2004). This was not seen in the contralateral paws. Interestingly, the hyperalgesia in both the inflamed hindpaw and the ipsilateral forepaw was more severe in rats with bilateral LC lesions than in sham-operated rats, suggesting that an inhibitory influence, emanating from the LC, extended ipsilaterally.

In humans, the effect of noxious stimulation on contralateral pain sensitivity has been studied over a range of stimulus modalities (e.g. thermal, electrical, ischemic) (Willer et al., 1984; Price and McHaffie, 1988; Kosek and Hansson, 1997) including brief inflammatory pain (Witting et al., 2000; Graven-Nielsen et al., 2002; de Tommaso et al., 2007; Shenker et al., 2008; Gibson et al., 2009). However, to the best of our knowledge, the
remote effect of a noxious stimulus on bilateral sensitivity to pain has been assessed in only two human studies. Unilateral tourniquet-induced left arm pain resulted in analgesia to pressure and heat which was similar in the left and right thigh in a sample of 18 participants (Tuveson et al., 2006). In a larger sample of participants, we reported bilateral analgesia to a sharp stimulus that was similar in the ipsilateral and contralateral forehead following cold-induced arm pain (Knudsen and Drummond, 2009). Analgesia to pressure-pain was also detected bilaterally in the forehead; however, this was more marked on the ipsilateral side suggesting that an inhibitory mechanism, perhaps coeruleospinal control, extended ipsilaterally. This finding was at odds with studies in rats that demonstrated hyperalgesia in the ipsilateral forepaw after hindpaw injection of the inflammatory agent carageenan (Tsuruoka et al., 2004), possibly because of differences in the stimulus modality (noxious cold versus inflammation) or duration of pain.

In the present study, sensory testing was performed on each side of the forehead in healthy humans during prolonged (48 hour) treatment of the forearm with topical capsaicin, an inflammatory agent. The aim was to investigate the remote effects of unilateral inflammatory limb pain at ipsilateral and contralateral sites in healthy humans.

Methods

Subjects

Seventeen healthy university students (3 males) with a median age of 27 years (range 18–41 years) participated in the study. Participants were excluded if they suffered from any medical problems including pain. Each participant provided written informed consent for the procedures, which were approved by the Murdoch University Human Research Ethics Committee.
Procedures

**Inflammatory hyperalgesia of the forearm.** After cleaning the skin with alcohol, two 13.5 cm² areas of the volar forearm were treated with the topical application of capsaicin cream (10% capsaicin dissolved in ethoxydiglycol and incorporated into a base of acetyl alcohol, stearic acid and fatty acid ester). The two areas were separated by 5 ± 2 cm with the lower area approximately 5 ± 2 cm from the wrist. The forearm on the non-dominant side of the body was treated in 50% of cases and the dominant forearm in the remaining cases. The capsaicin treatment was covered in bandages and left in place for 24 hours. The area of treatment was marked and a new amount of capsaicin was applied to the same cleaned skin for another 24 hours. A 45°C heat pack was placed on the treated areas (on top of the bandages) to rekindle pain at times of sensory assessments. Heating capsaicin treated areas reliably rekindles capsaicin-induced sensitivity (Koltzenburg et al., 1992; Dirks et al., 2003). Participants rated the pain intensity on a scale from 0 (no pain) to 10 (extremely severe pain) and also rated the distress associated with the pain in the forearm from 0 (no distress) to 10 (extremely severe distress).

**Sensory assessments.** Pain thresholds to firm pressure (PPT) and the extent of sharpness produced by a firm nylon bristle were assessed in the two areas of capsaicin application and in the equivalent areas of the contralateral forearm as well as on each side of the forehead. Pressure was applied gradually at intervals of 200 g using a spring loaded algometer with a rounded tip (1 cm in diameter). This was done to a maximum of 2.3 kg or until the participant felt pain. The mean value in each forearm was assumed as the PPT for that arm. In the forehead, pressure was applied at 80 g increments (Knudsen and Drummond, 2009). In participants who did not experience pain at 2.3 kg in the forearm, a
pressure-pain threshold of 2.3 kg was assumed. Sharpness was rated on a scale from 0 (not sharp) to 10 (stabbing) in response to a single application of the bristle (Filament 17, Senselab von Frey Aesthesiometer, Somedic Sales AB, Sweden). Sufficient force was applied to bend the bristle for 1 s (Knudsen and Drummond, 2009). Again the values obtained from the two sites in each forearm were averaged. The order of assessments was randomised between subjects to exclude order or time effects, but was kept constant within each subject to ensure that any change in sensitivity was not due to a change in the order of assessments.

**Trial sequence.** Participants were examined five times over a 48 hour period. In the morning of day one, sensory assessments were conducted at all sites before the first capsaicin application. In the afternoon (median time after application 6 hours, range 5.5-8 hours), sensory assessments were repeated in the forehead before and during heat stimulation. Participants reported the maximum pain and associated distress experienced since the previous session in addition to pain and distress levels before and during heat stimulation. These procedures were repeated the following morning (median time after application 24 hours, range 23-25.5 hours) before the capsaicin was re-applied, and were performed again in the afternoon (median time after application 30 hours, range 29.5-32 hours). These procedures were also conducted in the morning of day three (median time after application 48 hours, range 46-49.5 hours) after which the capsaicin was removed and a final assessment of sensitivity was performed at all sites in the arm and forehead.

**Statistical analysis.** Student’s t-tests were used to assess side differences in forehead sensitivity to pressure-pain and sharpness prior to testing as well as to assess differences in pain and distress responses between the two capsaicin applications. The extent of pain and
distress from the capsaicin and heat stimulation were investigated in Heating (before and during heating of the capsaicin-treated skin) x Time (the five assessments) analyses of variance. Side (treated forearm, untreated forearm) x Time (before capsaicin, after removal of capsaicin) analyses of variance for PPT and sharpness ratings assessed the development of hyperalgesia in the treated forearm. The influence of heating the capsaicin-treated skin on forehead sensations was investigated in Side (ipsilateral or contralateral to the capsaicin application) x Time (the five repeated measures) x Heating (before and during heating of the capsaicin-treated skin) analyses of variance for PPT and sharpness ratings. The Huynh-Feldt epsilon was used to correct for violations of sphericity. Changes across time points were investigated with simple contrasts, and student’s t-tests or analyses of variance were used as appropriate for post hoc analyses. In addition, Pearson’s correlations were performed between pain, distress ratings, sensations in the capsaicin-treated forearm (compared with the contralateral forearm) and changes in forehead sensitivity from before to after 48 hours of capsaicin treatment, to investigate whether the changes in forehead sensitivity were related to the pain intensity, distress and hyperalgesia caused by the capsaicin. Data are reported as the mean ± standard error of the mean.

Results

Symmetry of forehead sensations prior to capsaicin treatment

The absolute difference between the right and left side of the forehead to pressure-pain upon commencement of the experiment was 80 g or less in the majority of participants (88%) (range 0-200 g). There was no difference in 36% of participants. In the group as a whole, PPTs did not differ between the two sides [Mright = 637.60 ± 31.84 g, Mleft = 652.00 ± 30.64 g, t(24) = 0.86, not significant]. The absolute difference in sharp sensations
between the right and left side of the forehead was a rating of 1 or less in 96% of participants (range 0-4) with 52% reporting no difference in sensitivity to sharpness. The difference was not statistically significant \( M_{\text{right}} = 2.34 \pm 0.40, M_{\text{left}} = 2.71 \pm 0.38, t(24) = 1.91, \text{not significant} \).

**Pain and distress from the capsaicin**

A burning pain marked by a red flare developed in all participants. The most severe pain was reported by participants after the first application of capsaicin \( M = 7.53 \pm 0.46 \) with slightly less severe pain after the second application \( M = 6.65 \pm 0.62 \) \( t(16) = 2.11, p < 0.05 \). However, the two applications produced similar distress \( M_{\text{first}} = 5.09 \pm 0.73, M_{\text{second}} = 4.38 \pm 0.83, t(16) = 1.54, \text{not significant} \). The pain peaked 5-6 hours after each application \( M_{\text{first}} = 6.01 \pm 1.72 \text{ hours}, M_{\text{second}} = 4.62 \pm 1.26 \text{ hours}, t(16) = 0.70, \text{not significant} \).

The pain immediately before each assessment was significantly lower \( M = 2.63 \pm 0.64 \) than the most severe pain reported \( M_{\text{first and second application}} = 7.09 \pm 0.50 \) \( t(16) = 8.31, p < 0.001 \). Nonetheless, the heat stimulation successfully rekindled the pain \( M = 6.47 \pm 0.42 \) \( \text{main effect for Heating F}(1,16) = 95.10, p < 0.001 \) to a level similar to the most severe pain. Interestingly, a significant interaction between time and heating \( \text{F}(3,48) = 4.85, p < 0.01 \) revealed that the heat was less successful at rekindling pain after 48 hours of capsaicin than during previous sessions \( p < 0.01 \) (Fig. 1). No difference in the pain immediately before heat stimulation was observed across sessions (Fig. 1).

Distress ratings were also lower before each session \( M = 1.86 \pm 0.64 \) compared to when the pain was most severe \( M_{\text{first and second application}} = 4.74 \pm 0.74 \) \( t(16) = 5.02, p < 0.001 \). However, heat stimulation similarly rekindled distress \( M = 4.30 \pm 0.72 \) \( \text{main}
effect for Heating $F(1,16) = 38.51, p < 0.001$] to a level equivalent to when the pain was worst. Again a significant interaction between time and heating $[F(1.95,31.20) = 6.39, p < 0.01]$ revealed that the heat was less successful at inducing distress after 48 hours of capsaicin compared to previous sessions $[p < 0.01]$ (Fig. 1). The distress during assessments without heat stimulation was similar across all sessions (Fig. 1).

**Primary hyperalgesia following capsaicin**

As shown in Figure 2, PPTs were similar in the two forearms [main effect for Side $F(1,16) = 0.67$, not significant] and were unchanged in both forearms from before to after removal of the capsaicin 48 hours later [main effect for Time $F(1,16) = 1.07$, not significant, Time x Side interaction $F(1,16) = 3.37$, not significant]. Sharpness ratings were also similar in the two forearms before capsaicin treatment, but increased in the treated forearm $[\tau(16) = 2.83, p < 0.05]$, and not in the untreated forearm, after removal of the capsaicin (Fig. 2) [Time x Side interaction $F(1,16) = 9.85, p < 0.01$]. This resulted in a greater sensitivity to sharpness in the treated than the untreated forearm at this time $[\tau(16) = 3.54, p < 0.01]$, consistent with the development of primary hyperalgesia to punctate stimuli (Kilo et al., 1994).

**Change in forehead sensations to the capsaicin**

As shown in Figure 3, heating the capsaicin-treated skin altered forehead sensitivity to pressure-pain [Side x Time x Heating interaction $F(4,64) = 4.07, p < 0.01$]. Investigation of this interaction revealed that PPTs were unchanged across sessions when sensory assessments were performed without the application of heat (main effect for Time $F(4,64) = 1.71$, not significant), although a trend of an increase in PPTs was apparent. This was the case for both sides of the forehead [Time x Side interaction $F(4,64) = 1.44$, not significant].
However, when the pain was rekindled by heat, a significant interaction between time and side tested emerged \([F(4,64) = 5.86, p < 0.001]\). After 48 hours of capsaicin, participants reported a significant increase in PPTs in the ipsilateral forehead compared to baseline \([p < 0.01]\) [main effect for Time (ipsilateral forehead) \(F(4,64) = 5.49, p < 0.01\)]. This resulted in significantly higher PPTs in the ipsilateral forehead compared with the contralateral forehead at this time \([t(16) = 3.28, p < 0.01]\). PPTs did not change significantly in the contralateral side of the forehead [main effect for Time \(F(4,64) = 0.82, \text{not significant}\)].

Sharpness sensations decreased in the forehead after 6 hours of capsaicin \([p < 0.01]\) and remained at this level for the duration of the study [main effect for Time \(F(1.96,31.32) = 9.11, p < 0.01\)] (Fig. 4). This occurred irrespective of heat stimulation [Heating x Time interaction \(F(4,64) = 0.69, \text{not significant}\)] and to the same extent on both sides of the forehead [Heating x Time x Side interaction \(F(2.03,32.45) = 0.53, \text{not significant}\)]. Sharpness sensations were similar during assessments with and without heat stimulation [main effect for Heating \(F(1,16) = 2.22, \text{not significant}\)].

*Were changes in forehead sensitivity related to pain intensity, distress and hyperalgesia?*

Individual changes in forehead sensitivity to pressure-pain from before to after 48 hours of capsaicin generally appeared to be unrelated to pain, distress or sensations in the capsaicin-treated forearm (Table 1). On the other hand, the development of bilateral analgesia to sharpness, which persisted after 48 hours of capsaicin treatment, appeared to be related to greater pain and distress irrespective of heat stimulation.
Discussion

The aim of this study was to investigate the remote effects of unilateral inflammatory limb pain at ipsilateral and contralateral sites in healthy humans. We detected bilateral forehead analgesia to sharpness and ipsilateral forehead analgesia to pressure-pain.

Capsaicin causes an inflammatory response by releasing vasoactive peptides such as substance P and calcitonin gene-related peptide (CGRP) from the peripheral endings of primary afferent fibers (Holzer, 1988; Maggi and Meli, 1988; Saria et al., 1988). It initially excites (Kenins, 1982; Szolcsanyi, 1988) and sensitizes C nociceptors (Szolcsanyi, 1977; Baumann et al., 1991). Consistent with inflammation, a red flare (Carpenter and Lynn, 1981; Culp et al., 1989; Mohammadian et al., 1998), burning pain and primary hyperalgesia to punctate (sharp) stimulation (Kilo et al., 1994) developed in the capsaicin-treated forearm. However, hyperalgesia to pressure-pain was absent in the treated area after 48 hours of treatment, possibly because the capsaicin did not penetrate to nociceptors in deeper tissue or because of C-fiber desensitization to the capsaicin treatment (Lynn, 1990; Pini et al., 1990; Nagy et al., 1993). In support of the second possibility, hyperalgesia to heat decreased across the period of capsaicin treatment. Capsaicin-induced sensitivity to heat is mediated by sensitization of C fiber mechano-heat nociceptors (Konietzny and Hensel, 1983; LaMotte et al., 1992), and C fibers mediate capsaicin-induced pressure hyperalgesia (Culp et al., 1989). Only one participant failed to report pain below maximum pressure at the treated site thus tolerance levels above maximum pressure is unlikely to have masked a decrease in pressure-pain thresholds at this site. Interestingly, hyperalgesia to sharp stimuli persisted despite signs of desensitization to heat possibly because Aδ fibers signal sharpness hyperalgesia with only a minor contribution from C fibers (Ali et al., 2000;
Fitzek et al., 2001) or because hyperalgesia to sharpness was maintained by central sensitization (Kilo et al., 1994).

When triggered by nociceptive stimuli, DNIC inhibit the activity of wide dynamic range neurons in the dorsal horn (Le Bars et al., 1979a; Morton et al., 1987) and in the trigeminal nucleus caudalis (Dickenson et al., 1980; Murase and Kawakita, 2000) via a supraspinal loop (Le Bars et al., 1979b; Cadden et al., 1983) evident by a reduction in pain sensitivity remote from the inciting stimulus. This effect was demonstrated to a range of conditioning stimuli (e.g., thermal, mechanical, electrical and ischemic) (Pertovaara et al., 1982; Willer et al., 1984; Price and McHaffie, 1988; Kosek and Hansson, 1997; Bouhassira et al., 2003; Tuveson et al., 2006; Knudsen and Drummond, 2009) including capsaicin-induced pain (de Tommaso et al., 2007; Gibson et al., 2009). The inhibitory action of DNIC is widespread rather than localised. In rats, bilateral DNIC effects were recorded from wide dynamic range neurons in the spinal cord and trigeminal nucleus caudalis following hot water immersion of tail, muscle and paws (Bouhassira et al., 1990; Bouhassira et al., 1992). In humans, analgesia developed bilaterally to pressure in the thighs during tourniquet-induced arm pain (Tuveson et al., 2006) and to sharp sensations in the forehead during cold-induced hand pain (Knudsen and Drummond, 2009). Thus, DNIC probably accounted for the bilateral forehead analgesia to sharp stimuli in the present study.

Whether the extent of DNIC is related to the intensity of pain induced by the conditioning stimulus is uncertain (Lautenbacher et al., 2002; Le Bars, 2002; Baad-Hansen et al., 2005; Pud et al., 2005; Granot et al., 2008). However, general agreement exists that the intensity of the conditioning stimulus, albeit not necessarily the perceived intensity, is important in determining the DNIC outcome. The present study lends support for a relationship between the extent of DNIC and perceived pain as forehead analgesia to
sharpness was greater in those experiencing more pain. This is consistent with a previous study by our group (Knudsen and Drummond, 2009).

Stress-induced analgesia (SIA) may also have contributed to the bilateral forehead analgesia to sharpness. The well-documented generalised inhibitory effects of stress and anxiety (Chesher and Chan, 1977; Willer et al., 1981; Bandura et al., 1988; Gamaro et al., 1998) are mediated both by non-opioid and opioid mechanisms (Spiaggia et al., 1979; Watkins and Mayer, 1982; Tierney et al., 1991). Distress was associated with greater forehead analgesia to sharpness in the present study, providing support for an involvement of SIA in concert with DNIC. In a previous study in our laboratory, these two mechanisms also appeared to operate jointly following cold-induced limb pain, which caused bilateral forehead analgesia both to pressure and sharpness in association with pain and distress (Knudsen and Drummond, 2009).

Curiously, sensitivity to sharpness was not reduced in the contralateral forearm. Both contralateral hyperalgesia (Shenker et al., 2008) and contralateral analgesia (Graven-Nielsen et al., 2002; Gibson et al., 2009) were previously reported in response to capsaicin. Perhaps the lack of change in sensitivity to sharpness in the contralateral forearm reflects a competitive balance between excitatory and inhibitory processes. Many neurons in lamina VII of the spinal cord respond to noxious stimulation from either side of the body (Basbaum and Jessell, 2000), providing a possible location for a convergence between excitatory signals from the treated and contralateral forearm.

Ipsilateral forehead analgesia to pressure-pain developed in the present study. A similar response developed acutely during cold-induced limb pain (Knudsen and Drummond, 2009). The mechanism underlying this analgesic response is uncertain, but might involve coeruleospinal pain modulation (Knudsen and Drummond, 2009). The locus coeruleus (LC) inhibits nociceptive activity in dorsal horn neurons (Jones and Gebhart,
1986b) via bilateral noradrenergic projections (Westlund et al., 1983; Fritschy and Grzanna, 1990; Clark et al., 1991; Clark and Proudfit, 1992; Sluka and Westlund, 1992) to all segmental levels of the spinal cord (Proudfit and Clark, 1991). It does so via actions at α2-adrenoceptors (Jones and Gebhart, 1986a; 1986b). During unilateral hindpaw inflammation of rats, noradrenaline was released in the ipsilateral dorsal horn but not contralaterally (Tsuruoka et al., 1999). Tsuruoka et al. (2004) found shorter paw withdrawal latencies to heat not only in the inflamed hindpaw but also in the non-inflamed but hyperalgesic forepaw of rats with bilateral LC lesions compared to sham operated rats. As this was not observed in the contralateral hind- or forepaw, coeruleospinal pain modulation appeared to inhibit hyperexcitable nociceptive dorsal horn neuron activity ipsilaterally. Hence, this mechanism may have contributed to the development of ipsilateral forehead analgesia to pressure-pain in human studies, both during inflammation and to cold-induced pain (Knudsen and Drummond, 2009).

Why an ipsilateral spread of hyperalgesia developed during intramuscular carageenan-induced hindpaw inflammation in the rat (Tsuruoka et al., 2004), but not during topical capsaicin treatment in humans, is unclear. The two chemicals appear to exert their effects via similar mechanisms (activation and sensitization of C fibers) (Kocher et al., 1987; Baumann et al., 1991). Both an excitatory and a less dominant anti-nociceptive component were present during carageenan-induced hindpaw inflammation (Tsuruoka et al., 2004). It is tempting to speculate that the inhibitory component outweighed the facilitatory component during capsaicin-induced inflammation in the present study.

Alternatively, the difference might lie in the tissue affected (predominantly muscle in the rat studies and skin in the human studies). Indeed, an accumulating body of evidence suggests that pain from muscle and skin are processed differently. Intramuscular capsaicin injections induce a greater area of referred pain than intradermal capsaicin in healthy
humans (Witting et al., 2000) and brief low frequency input from C fibers in the muscle are more effective at producing a prolonged increase in the excitability of the flexion reflex (central sensitization) than cutaneous C fibers (Wall and Woolf, 1984). In some clinical populations (thalamic lesions, central post-stroke pain, complex regional pain syndrome), a loss of cutaneous sensation co-exists with the persistence or increase in pain to deep pressure (Riddoch, 1938; Mailis and Bennett, 2002; Drummond and Finch, 2006). Nociceptors from cutaneous tissue primarily innervate lamina I and II (Willis and Coggeshall, 1991) whereas muscle afferents predominantly project to laminae I and V (Craig et al., 1988; Mense and Craig, 1988; Ohtori et al., 2000). Moreover, different areas in the brain appear to be activated in response to cutaneous pain versus pain of deeper origin (Henderson et al., 2006). The dissociation between sharpness and pressure-pain sensations to conditioning stimuli in the present and a previous study (Knudsen and Drummond, 2009) provides further support for different central processing of skin and deep tissue sensibility.

Interestingly, some discrepancies appeared between the remote effects of inflammatory pain (the present study) and cold-induced pain in our previous study (Knudsen and Drummond, 2009). During cold-induced limb pain, pressure-pain sensitivity in the forehead decreased bilaterally, although the ipsilateral reduction was greater than the contralateral reduction (Knudsen and Drummond, 2009). The reason for the lack of the bilateral component to pressure-pain in the present study may lie in the sensitization of C fibers during capsaicin treatment (Baumann et al., 1991) which increases the input of C fibers to the dorsal horn. Repeated or persistent C fiber input to the dorsal horn has been associated with central sensitization – an enhanced response in dorsal horn neurons to normal input (Wall and Woolf, 1984; Woolf and Wall, 1986). This mechanism may underlie referred pain (Graven-Nielsen et al., 2002). Perhaps an enhanced response of
dorsal horn neurons to input from C fibers competed with inhibitory mechanisms at remote sites, resulting in a lack of change in sensitivity to pressure-pain remotely for most of the study. When C fiber desensitization began peripherally in the treated area, input to the spinal cord (and perhaps the sensitization of central dorsal horn neurons) may have decreased enough to shift the equilibrium toward analgesia in the ipsilateral forehead. Clearly more research is needed to investigate this possibility.

The time course of the forehead changes also varied greatly between the two studies (minutes in the cold pressor study and hours in the present study). The size or depth of the tissue affected (the entire hand in the cold pressor versus a small area of skin on the forearm in the capsaicin study) could underlie such differences.

The present study was performed in a young, educated and predominantly female population and thus may not be entirely representative of the general population. Nonetheless, the results replicate findings of activation of bilateral and ipsilateral pain inhibitory mechanisms following painful conditioning or inflammatory stimuli (Tsuruoka et al., 2004; Tuveson et al., 2006; Knudsen and Drummond, 2009). DNIC and SIA probably accounted for the development of bilateral analgesia to sharpness, whereas coeruleospinal pain modulation may have been involved in the ipsilateral analgesia to pressure-pain. These findings lend support to an increasing body of research that suggests that pain modulation involves unilaterally extending mechanisms in addition to local and generalized controls. Patients with complex regional pain syndrome experience hyperalgesia in the affected limb which often extends to the ipsilateral forehead (Drummond and Finch, 2006). Further elucidation of the inhibitory and facilitatory mechanisms that modulate ipsilateral pain processing may help to clarify the pathophysiology of this poorly understood condition.
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Table 1

Pearson’s correlations between pain, distress and hyperalgesia in the capsaicin-treated forearm (compared with the contralateral forearm) at 48 hours of capsaicin treatment and changes in forehead sensations (mean, asymmetry between the side ipsilateral and contralateral to treatment) from before to after 48 hours of capsaicin treatment

<table>
<thead>
<tr>
<th>Treated forearm</th>
<th>Changes in forehead sensations</th>
<th>Pressure-pain</th>
<th>Sharpness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No heat</td>
<td>Heat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Asymmetry</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td>0.07</td>
<td>-0.45#</td>
</tr>
<tr>
<td>Distress</td>
<td></td>
<td>0.15</td>
<td>-0.35</td>
</tr>
<tr>
<td>Pressure hyperalgesia</td>
<td></td>
<td>-0.17</td>
<td>0.23</td>
</tr>
<tr>
<td>Sharpness hyperalgesia</td>
<td></td>
<td>-0.18</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

*p < 0.09; *p < 0.05; **p < 0.01
Fig. 1. Forearm pain and distress ratings for 48 hours during capsaicin stimulation and at times of heat stimulation. Heat was less successful at rekindling pain and distress after 48 hours of treatment compared to previous sessions (** p < 0.01). Error bars represent standard errors and the arrow represents the initial application of capsaicin.
Fig. 2. PPTs and sharpness ratings for the capsaicin-treated and untreated forearm before and after 48 hours of capsaicin. PPTs did not change in either forearm whereas sharpness ratings increased in the treated (* p < 0.05) but not the untreated forearm resulting in greater sensitivity to sharpness in the treated than the untreated forearm (**) p < 0.01. Error bars represent standard errors.
Fig. 3. PPTs for sides of the forehead ipsilateral and contralateral to the capsaicin-treated forearm before and for 48 hours during treatment and during times of heat stimulation. PPTs increased significantly in the ipsilateral forehead after 48 hours of treatment (** p < 0.01) resulting in greater PPTs in the ipsilateral than contralateral forehead (** p < 0.01). Error bars represent standard errors and the arrow represents the initial application of capsaicin.
Fig. 4. Sharpness ratings for sides of the forehead ipsilateral and contralateral to the capsaicin-treated forearm before and for 48 hours during treatment and during heat stimulation. Sharpness ratings decreased bilaterally after 6 hours of treatment (** p < 0.01) and remained at this level for the duration of the study. Error bars represent standard errors and the arrow represents the initial application of capsaicin.
CHAPTER 8

REDUCTION OF ALLODYNA IN PATIENTS WITH COMPLEX REGIONAL PAIN SYNDROME: A DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF TOPICAL KETAMINE

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Pages: 37
Tables: 4
Figures: 4

Key words: Complex regional pain syndrome; topical ketamine; NMDA receptors; allodynia; hemilateral hyperalgesia
Abstract

A double-blind placebo-controlled crossover trial was used to determine the effects of topical ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, on sensory disturbances in 20 patients with complex regional pain syndrome (CRPS). On two occasions separated by at least one week, sensory tests to light touch, pressure, punctate stimulation, light brushing and thermal stimuli were performed in the symptomatic and contralateral limb and on each side of the forehead before and 30 minutes after 10% ketamine cream was applied to the symptomatic or healthy limb. Venous blood for plasma estimations of ketamine and norketamine was obtained one hour after application of the creams. Ketamine applied to the symptomatic limb inhibited allodynia to light brushing and hyperalgesia to punctate stimulation. Systemic effects of the ketamine are unlikely to account for this as plasma levels were below detectable limits. As touch thresholds were unchanged, NMDA receptors may contribute to sensory disturbances in CRPS via actions at cutaneous nociceptors. Allodynia and hyperalgesia were detected in the ipsilateral forehead to a range of stimuli (brushing, pressure, punctate stimulation, cold, heat, warmth). In several patients, ketamine treatment of the symptomatic limb inhibited allodynia to brushing the ipsilateral forehead, suggesting that the mechanism that mediates allodynia in the symptomatic limb contributed to allodynia at more remote sites. The present study shows promise for the use of topical ketamine as opposed to parenteral and oral forms which often result in undesirable side effects.
Introduction

Complex regional pain syndrome (CRPS) can develop after apparently trivial injury and is often associated with widespread sensory disturbances [21, 64, 77]. Unfortunately, the treatment of neuropathic pain states, including CRPS, remains a significant challenge [19]. Moreover, many of the commonly used orally administered drugs can cause significant central side effects such as somnolence and cognitive impairment with loss of patient compliance [30; 33]. A number of topical applications have been tried for neuropathic pain states, targeting peripheral receptor systems and pain mediators, but with mixed success [16; 17; 36; 39; 40; 41; 47; 48; 53; 59; 79; 84; 89; 94; 97].

Glutamatergic mechanisms are widely involved in excitatory neurotransmission, including nociception [7; 68; 88]. Of particular importance is the involvement of N-methyl-D-aspartate (NMDA) receptors in chronic pain states, including CRPS. As all major groups of glutamate receptor are found on nerve fibres in peripheral tissues [10], it would appear logical to attempt local peripheral block of NMDA receptors to reduce allodynia in CRPS. The general anaesthetic agent ketamine [18], and its major metabolite norketamine, have a significant non-competitive blocking action on NMDA receptors [1; 24]. Subanaesthetic dosage of ketamine provides worthwhile analgesia both in acute, postoperative and chronic pain states [4]. Trials of the use of ketamine in the treatment of neuropathic pain states have largely revolved around its intravenous administration [2; 3; 5; 11; 25-27; 29; 34; 37; 42; 49-51; 54; 69; 71; 80; 82; 93] but intramuscular [35] and subcutaneous infusions have also been tried [25; 67; 70]. Alternative routes of administration have included epidural [85], intrathecal [96], placement adjacent to the sympathetic chain [83], oral [15; 31; 75; 91] and topical application [12; 32; 41; 57; 60; 61; 73; 74; 81; 90]. Several randomised, double-blind,
placebo-controlled studies have reported on the reduction of allodynia following intravenous administration of ketamine [7; 25; 28; 29; 65] but literature on the topical use of ketamine is particularly sparse, mostly comprising case studies. To our knowledge, only one group has reported the effects of topical ketamine on pain and hyperalgesia in a double-blind, placebo-controlled trial. In this study neither ketamine 1% nor amitriptyline 2%, either separately or combined, were effective in patients with neuropathic pain, possibly because drug concentrations were suboptimal [60].

Topical administration aims to deposit drugs with localised activity in the outer layers of skin, thus minimizing systemic absorption and reducing unwanted central side effects [78]. For ketamine, these include vivid dreaming, dysphoria and alteration of cognition. The aim of the current study was to investigate the sensory effects of topical ketamine 10% in CRPS, particularly on allodynia. A double-blind placebo-controlled trial was used with simultaneous plasma estimations of ketamine and its principal metabolite. Sensory effects were investigated in the CRPS-affected limb and also in the forehead, to determine if the effects of ketamine were restricted to the site of application or whether topical ketamine also impeded the hemilateral sensory disturbances associated with CRPS [21].

Materials and Methods

Participants

Twenty sequential patients with features of CRPS (6 males, 14 females), attending a small private pain medicine centre, were studied. Each patient met the diagnostic criteria for CRPS [43] and the majority (17) met the more stringent criteria by Harden et al. [38]. Twelve had developed CRPS in an upper limb and eight in a lower limb. CRPS had developed after fractures (5 patients), soft tissue injury, or sprain (6 patients), surgery or needle insertion (3 patients). Four patients had developed pain
following infection, clotting, electric shock or anaphylactic reaction. In all, eighteen patients were classified CRPS Type 1 and two patients were classified CRPS Type 2 following direct injuries to an ulnar nerve. The pain had persisted for 2 months to 19.2 years (median duration 18 months). Sensory, autonomic and motor disturbances were reported by patients and noted during the initial physical examination (Table 1). Sensory disturbances to punctate stimulation and brushing in the symptomatic and healthy limbs were determined using the standard tests of sensation described below. The temperature of the first phalanx of each toe was determined in lower limb CRPS patients, whilst the equivalent was obtained in the fingers of patients with upper limb pain, using an infrared skin thermometer (Tempett IR Thermometer, Somedic Sales AB, Sweden) after the patient had rested quietly for at least 20 minutes in a room maintained at 20 ± 2°C. The Murdoch University Human Research Ethics Committee approved the study and written informed consent was obtained from each participant.

*Sensory testing*

All assessments were performed by the same examiner (LK) on the most hyperalgesic dorsal aspect of the symptomatic limb (lateral or medial hand or foot), as determined at the initial examination. Testing was performed at only one site in each limb to limit the duration of testing and thus decrease any effects of fatigue. If hyperalgesia did not differ between the lateral and medial sites, the lateral site was selected. The equivalent site was tested in the contralateral limb. Sensory testing was also conducted on each side of the forehead to determine remote effects of the ketamine.

*Light touch.* Threshold to touch was estimated by using thin Von Frey filaments (Senselab Aesthesiometer, Somedic Sales AB, Sweden). With closed eyes, patients indicated the site of stimulation on the symptomatic or healthy limb, once a sensation
was detected. The assessment started with mid-range filaments and thicker or thinner filaments were applied as required, until the detection threshold was established for each site. When detection was missed on at least two of three touches, this was determined to be at a level below the threshold for light touch. Participants were required to make similar distinctions for each side of the forehead.

*Pressure-pain thresholds.* Pressure-pain thresholds (PPT) were assessed with a rounded-tip (1 cm diameter) spring-loaded algometer [22]. Force was applied to each limb in increments of 200 gm to a maximum of 2.3 kg or until pain was reported. In the forehead, force was applied in 80 gm increments on each side. Some patients did not perceive pain at 2.3 kg. For these participants, a value of 2.3 kg was recorded as the pressure-pain threshold.

*Punctate stimulation.* Sharpness was rated at each site in response to a single application of a firm nylon bristle (Filament 17, Senselab von Frey Aesthesiometer, Somedic Sales AB, Sweden), which was tolerated by all patients. Ratings were given on a scale from 0 (not sharp) to 10 (stabbing). Sufficient force was applied to bend the bristle for 1 second. Wind-up to punctuate stimulation was investigated with three repeated applications of the bristle at 1-second intervals. The sharpness from the final application was recorded.

*Sensations evoked by light brushing.* Light stroking with a small brush (3-4 strokes backwards and forwards) was rated at each site as a normal or abnormal sensation. When the brushing evoked an abnormal sensation, participants gave a qualitative description of that sensation. Sensations with an element of pain (e.g., sharp, scratching, or uncomfortable sensations) were categorised as allodynia. Because of their
disparate quality, patients were not asked to rate the intensity of these sensations. Dull or numb sensations to brushing were also noted by two patients (Table 1) but were not regarded as allodynia.

**Thermal thresholds.** A thermal stimulator with a 2 cm diameter circular stimulating area operating on the Peltier principle was used to determine thermal thresholds. The contact probe was applied at a thermoneutral starting temperature of 32°C. The probe temperature was increased or decreased at a rate of 0.5 °C/sec to a maximum of 50°C or a minimum of 5°C. The following stimuli were presented sequentially: decreasing probe temperature until a cold sensation was detected; increasing probe temperature until a warm sensation was detected; decreasing probe temperature to the cold pain threshold; and increasing probe temperature to the heat pain threshold. For determination of cold and warm sensory thresholds, the subject was instructed to report as soon as a change of temperature was detected. For cold pain and heat pain thresholds, the subject was instructed to signal the first instance of pain. Some subjects did not detect cold pain sensations at 5°C; for these a value of 5°C was assumed as the cold pain threshold. Similarly, a heat pain threshold of 50°C was recorded for those who did not perceive heat pain at 50°C. Stimulation was rotated between each site until all sites had been tested two to four times (two assessments were considered sufficient if differences between presentations were equal to or less than 0.2°C). The average of the values for each sensation was considered to be the detection threshold for that sensation.

**Topical ketamine and placebo.** Absorption of topical agents can be influenced by vehicle composition [13]. Pluronic lecithin organogel (PLO), a microemulsion-based gel, was used in the composition of the cream to assist penetration of the stratum
corneum of the skin. It is a stable compound that shows no harmful effects when applied for prolonged periods [20; 46; 95]. The racemic form of ketamine hydrochloride 10% in PLO was used in the ketamine cream (Professional Compounding Centers of America, 9901 South Wilcrest, Houston, Texas, USA). The placebo contained the same PLO vehicle but without the addition of ketamine or any other active ingredient. The two creams were physically indistinguishable to patients and experimenters alike. A subgroup of patients (N = 5) attempted to identify the active cream following the trial but did so at a rate no better than chance. The 10% concentration of ketamine was chosen on the basis of pilot tests. For each patient, the active and placebo creams were randomly labelled A or B by the compounding pharmacist. Throughout the trial, access to the randomisation codes was available only to the pharmacist. One of the investigators (LK) applied 0.5 ml of either A or B cream to the symptomatic limb while 0.5 ml of the other cream was applied to the healthy limb. The amount of cream was restricted to minimise any systemic effects but was usually enough to cover the area of testing on the dorsum of the hand or foot as well as the neighbouring medial or lateral side of the appendage.

Blood samples. Venous blood was drawn 1 hour after the application of both topical agents for the first 10 patients during their initial trial. The blood was centrifuged for 10 minutes and the plasma was subsequently stored at -20°C until it was analysed for concentrations of ketamine and its main metabolite, norketamine [8].

Assay of ketamine and norketamine by high performance liquid chromatography. Plasma (1 ml) was spiked with ephedrine as an internal standard, alkalised with NaOH, and extracted with t-butyl methyl ether. The organic phase was back extracted into 0.05M HCl and aliquots of the HCl phase were injected onto the
HPLC column. Separation was performed on a Merck Chromolith® Performance column (100 mm x 4.6 mm id) using a mobile phase of 6% v/v acetonitrile in 50 mM K$_2$HPO$_4$ adjusted to pH 2.5 with H$_3$PO$_4$. The mobile phase was pumped at 2.5 mL/min and analytes were detected by their UV absorbance at 210nm. Calibration curves ranging from 1-20 µg/l were linear for both norketamine and ketamine. Intra-day (n=5) and inter-day (n=25) relative standard deviations for both ketamine and norketamine, measured at 5 µg/L, 50 µg/L and 200 µg/L ranged between 14.3% and 4.2%. The limit of quantitation was 1 µg/l for both analytes. The limits of detection were 0.5 µg/l and 0.7 µg/l for norketamine and ketamine, respectively.

**Trial sequence.** Participants underwent two separate sensory assessments with application of the topical creams, separated by at least one week (median 1 week, range 7 days to 23 days) to allow for the metabolic removal of any active ingredients from the skin. The sensory assessments were performed before and 30 minutes after the application of the topical creams. This timing was determined after pilot testing. To rule out systematic effects of testing, the order of the assessments was randomised between participants. However, the order of the assessments was kept constant within each participant to ensure that the active and placebo conditions were identical.

**Statistical approach**

Although some of the score distributions did not fit a normal bell-shaped curve, logarithmic transformations did not necessarily improve the score distribution significantly and generally did not strengthen statistical effects. Therefore, where appropriate, a nonparametric statistical approach was employed. Before the creams were applied, differences in pain and sensory thresholds between the symptomatic and healthy limbs were investigated with Wilcoxon’s matched-pairs signed-ranks test. As analysis of
variance generally is robust to violations of normality, effects of ketamine on limb pain were investigated in Drug (ketamine versus placebo) x Side (symptomatic versus healthy side) x Pre-Post (the change from before to after the application of the creams) analyses of variance. The effect of most interest was the Drug x Side x Pre-Post interaction, as it tested whether ketamine applied to the symptomatic limb inhibited sensory disturbances in that limb. More generally, the Drug x Pre-Post interaction tested whether ketamine inhibited painful sensations locally when applied to either limb. Wilcoxon’s test was employed to investigate significant interactions. For clarity, effects of ketamine on sensory disturbances in the forehead were investigated in separate analyses. The association between sensory disturbances in the symptomatic limb and sensory disturbances in the ipsilateral forehead was investigated with Spearman’s correlation coefficient.

Results

Effect of topical ketamine on sensory disturbances in the symptomatic limb

Before the creams were applied, sensory disturbances in the symptomatic limb included allodynia to brushing and hyperalgesia to punctate stimulation and pressure (Table 2). In addition, the touch threshold, assessed with von Frey hairs, was greater in the symptomatic than healthy limb.

Pain in the symptomatic limb averaged $4.9 \pm 0.5$ on a 0-10 scale (moderately painful), and did not change after the application of the ketamine cream or placebo. Nor did the touch threshold change significantly. Nevertheless, the ketamine cream inhibited allodynia to lightly brushing the symptomatic limb [Drug x Side x Pre-Post interaction $F(1,19) = 4.41, p = 0.049$] (Figure 1). Ketamine also inhibited pain evoked by pricking the skin three times with a firm von Frey bristle [Drug x Pre-Post interaction $F(1,15) =$
The inhibitory effect was greatest when ketamine was applied to the symptomatic limb, but ketamine applied to the healthy limb also inhibited pin-prick sensations slightly in that limb (Figure 2). Results were similar after the skin was pricked once [Drug x Pre-Post interaction $F(1,15) = 3.63$, $p = 0.076$].

The pressure-pain threshold increased in the symptomatic limb after ketamine or placebo cream was applied to the symptomatic limb [Side x Pre-Post interaction $F(1,19) = 5.33$, $p = 0.032$] (Figure 3), and the warmth threshold increased in both limbs when the creams were applied [from 36.1 ± 0.9 °C to 37.2 ± 0.9 °C, Pre-Post main effect $F(1,18) = 4.56$, $p = 0.047$]. However, the cool, cold-pain and heat-pain thresholds did not change.

Effect of topical ketamine on sensory disturbances in the forehead

Allodynia to brushing and hyperalgesia to punctate stimulation, pressure, cold and heat were detected on the symptomatic side of the forehead before the creams were applied to the limbs (Table 3). In addition, sensitivity to warmth was greater on the symptomatic side of the forehead than on the non-symptomatic side. As shown in Table 4, sensory disturbances in the forehead were associated with heightened tactile sensitivity in the symptomatic limb, and with hyperalgesia to punctate and thermal stimuli.

In two patients, hypoesthetic sensations were evoked by lightly brushing the symptomatic limb but not the healthy limb, both before and after the ketamine and placebo creams were applied. In one of these patients, brushing the forehead also evoked a similar sensation on the symptomatic side before ketamine was applied to the symptomatic limb; this sensation persisted after the cream was applied. In the other 18 patients, brushing the limbs and forehead provoked either a normal sensation or allodynia. The ketamine cream inhibited allodynia to lightly brushing the forehead
[Drug x Pre-Post interaction F(1,19) = 4.75, p = 0.042]. The inhibitory effect was greater when ketamine than placebo was applied to the symptomatic limb (Figure 4).

Sensitivity to cool and warm sensations decreased slightly on both sides of the forehead after the creams were applied. In particular, the cool detection threshold decreased from 29.7 ± 0.3 °C to 29.1 ± 0.5 °C [Pre-Post main effect F(1,18) = 4.52, p = 0.048], whereas the warmth detection threshold increased from 34.9 ± 0.5 °C to 35.3 ± 0.5 °C [Pre-Post main effect F(1,18) = 5.22, p = 0.035]. Conversely, the heat pain threshold decreased from 39.7 ± 0.6 °C to 39.1 ± 0.7 °C [Pre-Post main effect F(1,18) = 4.79, p = 0.042]. The other sensory thresholds remained unchanged.

Detection threshold for Ketamine and Norketamine

Neither ketamine nor norketamine could be detected in any of the plasma samples from the first 10 patients assessed in the trial. Therefore, assays were discontinued for the remainder of the study. The threshold for detection was 0.7 µg/l for ketamine and 0.5 µg/l for norketamine.

Discussion

The primary aim of this study was to determine whether topical ketamine inhibited sensory disturbances in the symptomatic limb of patients with CRPS. We found evidence of this for allodynia and punctate hyperalgesia. The effect was greatest in the symptomatic limb, but ketamine applied to the healthy limb also slightly inhibited sharp sensations in that limb. This appeared to involve a local mechanism because ketamine applied to the healthy limb had no effect on allodynia or punctate hyperalgesia in the symptomatic limb.
Allodynia to brushing the skin and punctate hyperalgesia to sharp stimulation is mediated by sensitized spinal nociceptive and wide dynamic range neurons that receive input from nociceptive A-delta fibres and non-nociceptive A-beta fibres [55; 56]. However, our findings suggest that a peripheral mechanism involving NMDA receptors also contributed to these sensory disturbances in our CRPS patients. This mechanism appeared to involve nociceptors because touch thresholds remained unchanged after the topical ketamine treatment. It did not seem to entail a systemic mechanism, because ketamine applied to the healthy limb was ineffective. Moreover, plasma levels of ketamine and its active metabolite, norketamine, were below the limits of detection after the creams were applied. Plasma levels of ketamine above 150 µg/l have previously been shown to cause pain threshold elevation [9; 92]. In our study the threshold for detection of ketamine was substantially lower, at 0.7 µg/l.

NMDA- and related ionotropic glutamate receptors are present on peripheral primary afferent neurons in the hairy and glabrous skin of rats [44] and in the hairy skin of humans [52]. These glutamate receptor populations are up-regulated in inflamed human skin [86] and appear to be involved in sensitizing primary afferent nociceptors during inflammation and tissue injury [6, 23, 45]. As NMDA increases the excitability of thermal nociceptors in animal models of inflammation, [23], we expected that the NMDA antagonist ketamine would inhibit thermal hyperalgesia in our CRPS patients. However, the cold-pain and heat-pain thresholds remained unchanged, implying that NMDA receptor blockade after the topical ketamine treatment was insufficient to decrease the activity of thermal nociceptors within the timeframe of the experiment. A higher concentration of ketamine and a longer delay before testing (to permit greater entry of ketamine into the skin) could be employed to investigate this possibility.

Sensitivity to warmth decreased in both limbs when the creams were applied, and sensitivity to cool and warm sensations decreased in the forehead. Conversely,
sensitivity to heat pain increased on both sides of the forehead after the ketamine cream was applied to either limb. These changes are more likely to reflect a reduction in perceptual acuity due to fatigue or effects of repeated testing than a systemic effect of ketamine, because neither ketamine nor norketamine were detected in plasma samples after the creams were applied. The pressure-pain threshold increased in the symptomatic limb irrespective of whether ketamine cream or placebo was applied to the symptomatic limb, possibly for similar reasons.

CRPS is associated with hemisensory disturbances that extend to the face [21; 76; 77; 87]. Rommel et al. [77] reported that sensory impairment to light touch, heat-pain, cool and warmth extended hemilaterally to the face in 30% of patients, whereas facial sensation was symmetrical in patients with sensory impairment limited to the affected limb. Although hypoalgesia in the symptomatic limb was associated with hypoalgesia on the symptomatic side of the forehead in a few of our patients, in most cases allodynia to brushing and hyperalgesia to pressure, punctate stimulation, cold and heat were detected on the symptomatic side of the forehead. In addition, this site was generally more sensitive to warmth than contralaterally. In a previous study of sensory disturbances in CRPS, we detected hyperalgesia to deep pressure on the symptomatic side of the forehead in the majority of patients; in addition, hyperalgesia to punctate stimulation extended ipsilaterally to the forehead in patients with punctate hyperalgesia in the symptomatic limb [21]. For unknown reasons, a greater range of sensory modalities was disrupted on the symptomatic side of the forehead in the present cohort of patients; this might have been a sampling effect or possibly was due to greater precision of measurement as measures were averaged across two sessions in the present study. In general, hyperalgesia in the symptomatic limb was associated with hyperalgesia on the symptomatic side of the forehead, implying mediation by a similar
mechanism (e.g., sensitization of spinal or supraspinal nociceptive neurons or disruption of central pain modulating processes).

Curiously, in a few patients ketamine cream applied to the symptomatic limb inhibited allodynia to lightly brushing the forehead. As this was a double-blind placebo-controlled trial and the effect was limited to allodynia, we are confident that this was not due to expectancy or social desirability biases. Clearly, the finding needs to be confirmed in a larger sample of patients. However, it is tempting to speculate that the mechanism that mediated allodynia in the symptomatic limb also contributed to allodynia at more remote sites. For example, disruption of central pain modulating processes might not only increase the excitability of sensitized spinal nociceptors but might also sensitize supraspinal nociceptive neurons that receive convergent hemilateral input (e.g., in the thalamus or somatosensory cortex). Cortical processing of input from the symptomatic limb is disrupted in CRPS [58; 62; 63; 72], with heightened cortical responses to noxious stimuli and shrinkage of representation of the symptomatic limb in the somatosensory cortex. This cortical reorganization might account for referred pain in CRPS [66], and might also explain why a reduction of allodynia in the symptomatic limb after the topical ketamine treatment was sometimes accompanied by a reduction of allodynia on the symptomatic side of the forehead.

The strengths of this study include the double-blind placebo-controlled crossover design, confirmation that ketamine did not enter the bloodstream in detectable concentrations, and the psychophysical assessment of multiple sensory modalities. However, as only one concentration of ketamine was employed, only a single dose was administered, and effects of ketamine were assessed at only one time point, further controlled studies are needed to determine whether the therapeutic effects of ketamine in CRPS are limited to dynamic allodynia and punctate hyperalgesia or also include other forms of hyperalgesia.
Parenteral and oral forms of ketamine have shown some promise for treating the burning pain and exquisite skin hypersensitivity of CRPS and other chronic pain states associated with nerve injury [42]. However, administration by these routes is limited by central side effects such as hallucinations and nightmares. Frequent abuse of ketamine can even cause long term memory impairment [14]. In open studies of topical ketamine, therapeutic effects appeared to strengthen with repeated applications [12; 32; 61; 74; 90]. As topical ketamine is simple and inexpensive to use, and systemic absorption appears to be minimal, further exploration of the therapeutic potential of topical NMDA blockers in CRPS would be welcome.

In conclusion, topical ketamine does not lead to pain reduction in patients with CRPS but does cause a reduction in allodynia, a most unpleasant aspect of this condition. Future treatment protocols could be expanded, to use topical ketamine for patients who manifest allodynia, as an adjunct to sensory-motor retraining programs and other more traditional forms of treatment.
Conflicts of interest

None of the authors has a conflict of interest with the contents of this paper.

Acknowledgements

This study was supported by the Australian and New Zealand College of Anaesthetists and the National Health and Medical Research Council of Australia. We wish to thank Professor Ken Ilett and Dr Madhu Page-Sharp, Pharmacology Unit, School of Medicine and Pharmacology, University of Western Australia for performing the ketamine assays and Mr Tony Accordino for compounding the ketamine and placebo creams.
References


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Table 1

Sensory, vasomotor/sudomotor, and motor/trophic disturbances in CRPS patients

<table>
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<tr>
<th>Limb</th>
<th>Pain duration (months)</th>
<th>Sensory</th>
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<td></td>
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<td>Hyperalgesia</td>
<td>Allodynia</td>
<td>Temp. sensation</td>
<td>ΔT (°C)</td>
</tr>
<tr>
<td>1. F, 59</td>
<td>RU 24</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>0.46</td>
</tr>
<tr>
<td>2. F, 35</td>
<td>RU 19</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>hot/cold</td>
<td>0.40</td>
</tr>
<tr>
<td>3. F, 51</td>
<td>RL 125</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>hot/cold</td>
<td>-0.26</td>
</tr>
<tr>
<td>4. M, 45</td>
<td>LL 6</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>0.18</td>
</tr>
<tr>
<td>5. F, 54</td>
<td>LU 27</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>-0.04</td>
</tr>
<tr>
<td>6. M, 20</td>
<td>RL 2</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>-1.34</td>
</tr>
<tr>
<td>7. F, 27</td>
<td>RL 17</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>-2.96</td>
</tr>
<tr>
<td>8. F, 37</td>
<td>LL 3</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>-3.82</td>
</tr>
<tr>
<td>9. F, 44</td>
<td>LU 26</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>-0.36</td>
</tr>
<tr>
<td>10. M, 50</td>
<td>RU 230</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>hot</td>
<td>-1.14</td>
</tr>
<tr>
<td>11. M, 48</td>
<td>LU 23</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>-0.37</td>
</tr>
<tr>
<td>12. F, 35</td>
<td>RU 10</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>0.44</td>
</tr>
<tr>
<td>13. F, 38</td>
<td>RU 57</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>0.04</td>
</tr>
<tr>
<td>14. F, 20</td>
<td>LU 2</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>hot/cold</td>
<td>0.60</td>
</tr>
<tr>
<td>15. M, 51</td>
<td>RU 129</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>0.46</td>
</tr>
<tr>
<td>16. M, 23</td>
<td>LU 6</td>
<td>hyperalgesia</td>
<td>alldynia</td>
<td>cold</td>
<td>-0.02</td>
</tr>
<tr>
<td>No.</td>
<td>Age</td>
<td>Sex</td>
<td>Extremity</td>
<td>Symptom</td>
<td>Temperature</td>
</tr>
<tr>
<td>-----</td>
<td>------</td>
<td>-----</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>17</td>
<td>F, 31</td>
<td>RU</td>
<td>13</td>
<td>hyperalgesia</td>
<td>hot/cold</td>
</tr>
<tr>
<td>18</td>
<td>F, 51</td>
<td>RL</td>
<td>10</td>
<td>hyperalgesia</td>
<td>hot</td>
</tr>
<tr>
<td>19</td>
<td>F, 41</td>
<td>LU</td>
<td>118</td>
<td>hyperalgesia</td>
<td>hot</td>
</tr>
<tr>
<td>20</td>
<td>F, 36</td>
<td>LL</td>
<td>11</td>
<td>hyperalgesia</td>
<td>cold</td>
</tr>
</tbody>
</table>

Symptom history as reported by patients. Signs of disturbances noted during the initial physical examination are italicized in bold. *Limb* LU, left upper extremity; RU, right upper extremity; LL, left lower extremity; RL, right lower extremity. *Sensory disturbances* reported by patients included hyperalgesia, allodynia and numbness. Numbness was reported by all but two patients (Nos. 4 and 10). Sensory disturbances noted during an initial physical examination included hyperalgesia to punctuate stimulation with a firm bristle (a sharpness rating (0-10) of at least 2 higher in the affected than the unaffected limb indicated hyperalgesia) and allodynia to brushing the skin with a light brush (an uncomfortable or painful sensation indicated allodynia). Two patients reported a numb sensation to the brushing (Nos. 9 and 11). *Vasomotor and sudomotor disturbances* reported by patients were asymmetrical temperature sensations, dyschromia and hyperhidrosis. Patients reported whether they perceived their limb to be cold or hot. Four patients reported that the limb would at times appear cold and other times hot. $\Delta T$, temperature asymmetry between the affected and unaffected limb as averaged for the first phalanx of each toe (lower limb patients) or each finger (upper limb patients). Negative values indicate that the affected limb was cooler than the unaffected limb. Swelling was reported by all patients. *A decreased range of movement* was observed and reported by all patients. Other *motor disturbances* reported by patients included weakness (all patients), tremor and dystonia. *Trophic changes* (hair, nails, skin) varied greatly between patients.
Table 2

Sensory thresholds and allodynia in the symptomatic and healthy limbs before ketamine and placebo creams were applied to the symptomatic limb

<table>
<thead>
<tr>
<th></th>
<th>Mean ± S.E.</th>
<th>Wilcoxon’s Z</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptomatic</td>
<td>Healthy</td>
</tr>
<tr>
<td>Touch (von Frey units)</td>
<td>10.3 ± 0.9</td>
<td>8.8 ± 0.4</td>
</tr>
<tr>
<td>Pressure (grams)</td>
<td>321 ± 82</td>
<td>1101 ± 116</td>
</tr>
<tr>
<td>Brushing (% with allodynia)</td>
<td>85%</td>
<td>10%</td>
</tr>
<tr>
<td>Sharpness (one application)</td>
<td>5.0 ± 0.7</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>Sharpness (three applications)</td>
<td>5.7 ± 0.7</td>
<td>3.7 ± 0.4</td>
</tr>
<tr>
<td>Cool threshold (°C)</td>
<td>26.2 ± 1.4</td>
<td>27.9 ± 0.9</td>
</tr>
<tr>
<td>Warmth threshold (°C)</td>
<td>36.6 ± 1.5</td>
<td>36.2 ± 0.6</td>
</tr>
<tr>
<td>Cold-pain threshold (°C)</td>
<td>19.0 ± 2.3</td>
<td>16.0 ± 1.5</td>
</tr>
<tr>
<td>Heat-pain threshold (°C)</td>
<td>39.9 ± 0.9</td>
<td>41.7 ± 0.6</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01; *** p < 0.001
Table 3

Sensory thresholds and allodynia in the forehead ipsilateral and contralateral to the symptomatic limb before ketamine and placebo creams were applied to the symptomatic limb

<table>
<thead>
<tr>
<th></th>
<th>Mean ± S.E.</th>
<th>Wilcoxon’s Z</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipsilateral side</td>
<td>Contralateral side</td>
</tr>
<tr>
<td>Touch (von Frey units)</td>
<td>5.0 ± 0.7</td>
<td>4.6 ± 0.6</td>
</tr>
<tr>
<td>Pressure (grams)</td>
<td>398 ± 44</td>
<td>524 ± 33</td>
</tr>
<tr>
<td>Brushing (% with allodynia)</td>
<td>60%</td>
<td>5%</td>
</tr>
<tr>
<td>Sharpness (one application)</td>
<td>5.1 ± 0.5</td>
<td>3.7 ± 0.5</td>
</tr>
<tr>
<td>Sharpness (three applications)</td>
<td>4.9 ± 0.5</td>
<td>3.9 ± 0.5</td>
</tr>
<tr>
<td>Cool threshold (°C)</td>
<td>30.3 ± 0.2</td>
<td>29.5 ± 0.5</td>
</tr>
<tr>
<td>Warmth threshold (°C)</td>
<td>34.4 ± 0.4</td>
<td>35.8 ± 0.6</td>
</tr>
<tr>
<td>Cold-pain threshold (°C)</td>
<td>24.7 ± 1.3</td>
<td>22.5 ± 1.3</td>
</tr>
<tr>
<td>Heat-pain threshold (°C)</td>
<td>38.7 ± 0.7</td>
<td>40.8 ± 0.6</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01; *** p < 0.001
Table 4

Association (Spearman’s rank-order correlation coefficient) between sensory disturbances in the symptomatic limb and asymmetry of sensations in the forehead

<table>
<thead>
<tr>
<th>Ipsilaterial versus contralateral side of the forehead</th>
<th>Sensations in the symptomatic limb (compared with the healthy limb)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Loss of touch</td>
</tr>
<tr>
<td>Loss of touch</td>
<td>.286</td>
</tr>
<tr>
<td>Pressure hyperalgesia</td>
<td>-.483*</td>
</tr>
<tr>
<td>Allodynia to brushing</td>
<td>-.390</td>
</tr>
<tr>
<td>Sharp – 1 rating</td>
<td>-.669***</td>
</tr>
<tr>
<td>Sharp – 3 rating</td>
<td>-.574*</td>
</tr>
<tr>
<td>Reduced cool sensitivity</td>
<td>-.107</td>
</tr>
<tr>
<td>Reduced warm sensitivity</td>
<td>-.312</td>
</tr>
<tr>
<td>Cold hyperalgesia</td>
<td>-.349</td>
</tr>
<tr>
<td>Heat hyperalgesia</td>
<td>-.608**</td>
</tr>
</tbody>
</table>

* p <0.05; ** p < 0.01; *** p < 0.001
Fig. 1. Proportion of patients with allodynia (± S.E.) to lightly brushing the symptomatic and healthy limbs before and after the application of 10% ketamine cream and placebo. Allodynia in the symptomatic limb decreased significantly after the ketamine cream was applied (* p < 0.01, Wilcoxon’s test).
Fig. 2. Sharpness ratings (± S.E.) to punctate stimulation with a firm von Frey bristle before and after the application of 10% ketamine cream and placebo to the symptomatic and healthy limbs of patients who reported that the bristle induced a sharp sensation in the symptomatic limb (i.e., the rating was greater than 0 before the cream was applied). When the bristle was applied three times at intervals of approximately 1 second (N = 16), sharpness ratings decreased after the ketamine cream was applied to the symptomatic limb (# \( p < 0.1 \), Wilcoxon’s test). Sharpness ratings to a single application of the bristle (N = 16) also decreased after the ketamine cream was applied to the healthy limb (# \( p < 0.1 \), Wilcoxon’s test).
Fig. 3. Pressure-pain thresholds (± S.E.) in the symptomatic and healthy limbs before and after the application of 10% ketamine cream and placebo.

The pressure-pain threshold increased in the symptomatic limb after the ketamine cream was applied either to the symptomatic or healthy limb (* p < 0.05, Wilcoxon’s test).
Fig. 4. Proportion of patients with allodynia (± S.E.) to lightly brushing the forehead ipsilateral or contralateral to the symptomatic limb before and after the application of 10% ketamine cream or placebo to the symptomatic limb. Allodynia on the ipsilateral side of the forehead decreased after the ketamine cream was applied to the symptomatic limb (# p < 0.1, Wilcoxon’s test) but did not change after the placebo cream was applied to the symptomatic limb.
CHAPTER 9
IPSILATERAL AUDITORY STARTLE ENHANCES HYPERACUSIS AND LIMB PAIN IN COMPLEX REGIONAL PAIN SYNDROME

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Pages: 29
Tables: 5
Figures: 1

Key words: complex regional pain syndrome; pain laterality; locus coeruleus; diffuse noxious inhibitory controls; stress-induced analgesia
Abstract

Patients with complex regional pain syndrome (CRPS) often demonstrate hemilaterial sensory disturbances and brain imaging changes in the contralateral sensory and motor cortices. This might indicate unilateral disturbances in nociceptive pathways. Unlike healthy controls, CRPS pain is aggravated, not inhibited, by startle with a loud tone. This is consistent with dysfunction of central inhibitory pain control. To determine whether such dysfunction is predominantly unilateral, we investigated whether the response was more pronounced during startle in the ipsilateral than the contralateral ear. Twenty-eight CRPS patients rated limb pain from 0 (no pain) to 10 (extremely severe pain) at 5 s intervals before and for 30 s after startle with a loud tone in each ear, and also rated auditory discomfort. Startle aggrivated limb pain in 21 patients (75%), had no effect in six patients and inhibited limb pain in one patient. The pain increase was greater to ipsilateral than contralateral startle. Patients with increased pain during startle reported greater auditory discomfort than non-responders, particularly to ipsilateral startle. These findings suggest neuronal hyperexcitability both in the sensory and auditory system in cortical or subcortical areas that process sensations from the CRPS-affected side of the body.
Introduction

The causalgic pain of complex regional pain syndrome (CRPS) is highly sensitive to acoustic stimuli and emotional excitement [13; 28; 39]. Although sensory-sympathetic coupling in the CRPS-affected limb may contribute to this, startle stimuli can still evoke limb pain after peripheral sympathetic blockade [14]. Thus, additional mechanisms appear to be involved.

CRPS is associated with heightened activity in the cortical nociceptive networks that process signals from the CRPS-affected limb [35; 37; 41]. Moreover, pain and sensory disturbances often spread beyond the limb, usually in a hemilateral distribution [15; 42; 48]. Together, such findings imply disruption of pain modulation at sites of somatosensory convergence within the central nervous system – for example, in the medullary reticular formation, thalamus or cerebral cortex. In the current study, a startle stimulus (a loud tone) was presented sequentially on the affected and unaffected side of patients with CRPS. We hypothesized that stimuli presented on the CRPS-affected side would evoke greater increases in limb pain than contralateral stimuli, due to ipsilateral excitatory influences on sensitized nociceptive networks.

Method

Participants

The sample consisted of 5 men and 23 women aged between 15 and 59 years (mean age 41.4 years) attending a pain medicine clinic. All patients met the IASP criteria for CRPS I (26 patients) or CRPS II (2 patients), and all but one met the more stringent criteria of Harden and colleagues [21]. Patients with hearing difficulties were excluded from the
study. Fourteen patients suffered from upper limb pain and 14 from lower limb pain. CRPS had begun after a fracture (10 patients), soft-tissue injuries such as sprains, tendonitis, bursitis or dislocation (7 patients), surgery (3 patients), nerve lesion (2 patients) or infection (2 patients). Another four patients had developed CRPS following an injection, electric shock, anaphylactic reaction or a non-occlusive blood clot. Pain had persisted between 2 months and 19.2 years (median 3.4 years). Twenty-two patients took analgesics, anticonvulsants and/or anti-depressants and 6 patients were medication-free. Patients continued routine medication during the trial due to ethical and practical concerns relating to discontinuation of medication. Sensory, autonomic and motor disturbances were reported by patients and noted during a physical examination by a medically-trained pain specialist, and sensory disturbances in the CRPS-affected limb were investigated further using psychophysical procedures (Table 1). Each participant gave their written informed consent for the procedures which had been approved by the local ethics committee.

Procedures

Sensory disturbances in the symptomatic limb and the forehead. Pressure-pain thresholds (PPT) and the intensity of sharpness evoked by a firm nylon bristle [29] were measured in the symptomatic limb and the contralateral healthy limb and on each side of the forehead. To obtain PPTs, a spring-loaded algometer with a rounded tip (1 cm in diameter) was applied in 200 g steps on each limb and in 80 g steps on each side of the forehead to a maximum of 2.3 kg or until the participant reported pain. Sharpness was rated on a scale from 0 (not sharp) to 10 (stabbing) in response to a single application of a bristle (Filament 17, Senselab von Frey Aesthesiometer, Somedic Sales AB, Sweden), which was applied with enough force to bend it for 1 s.
**Startle.** A loud tone (100 Hz, 102 dBA, 0.5 s duration) was delivered through headphones to one ear. To investigate the effect of the tone on pain in the symptomatic limb, ratings of pain intensity were obtained on a scale from 0 (no pain) to 10 (extremely severe pain) [13]. Participants then rated auditory discomfort induced by the tone on a scale from 0 (not unpleasant) to 10 (extremely unpleasant).

**Sweating and blood flow.** Changes in sweating and blood flow in response to the startle stimuli were assessed in the final 11 patients studied (7 with upper limb pain and 4 with lower limb pain). To measure electrodermal activity (which reflects sweating), two silver-silver chloride Beckman cup electrodes (0.8 cm diameter) were filled with conducting paste and attached to the CRPS-affected and contralateral healthy limb [13]. In upper limb patients, the electrodes were placed on the middle phalanx of the index and third finger (palmar surface) whilst they were attached to the second and third toe in lower limb patients (plantar surface). The maximum increase in electrodermal activity 10 s after the startle stimulus was measured in both limbs. Changes in digital blood flow were monitored using pulse transducers (photoplethysmographs, Grass Instruments Company, Quincy, MA) attached with Velcro straps to a finger (upper limb patients) or a toe (lower limb patients) of the symptomatic and healthy limbs [13]. The blood flow response to startle was defined as the mean pulse amplitude for 10 s after startle, expressed as a proportion of the mean pulse amplitude for 10 s prior to startle.

**Trials.** After PPTs and sharpness were measured in the limbs and forehead, the loud tone was presented four times in the following sequence: to the first ear (then wait 2 minutes); second ear (wait 5 minutes); second ear again (wait 2 minutes); first ear. The first startle stimulus was presented on the CRPS-affected side in 50% of participants. Pain in the
CRPS-affected limb was rated every 5 s for 15 s before and for 30 s after each tone. Patients were warned about the appearance of the tone to reduce any painful effects of sudden movement. After the pain ratings had been completed, patients rated auditory discomfort.

Statistical analysis. Due to violations of normality, Wilcoxon’s matched-pairs signed-ranks tests were used to assess differences in sensitivity to pressure-pain and sharpness between the affected and unaffected limbs, and between the ipsilateral and contralateral sides of the forehead. Wilcoxon’s tests were also employed to assess the difference in auditory discomfort to ipsilateral versus contralateral startle. The mean pain intensity for 15 s before ipsilateral startle and for 15 s before contralateral startle was calculated, and ratings were averaged across stimuli presented to the same ear for each subsequent time point. A 2 (ipsilateral startle, contralateral startle) x 8 (consecutive time-points) repeated measures analysis of variance assessed changes in pain in the CRPS-affected limb to startle stimuli in the contralateral versus ipsilateral ear. The Huynh-Feldt epsilon was used to correct for violations of sphericity (i.e., when scores at one set of times were more closely related than scores at another set of times). Changes in electrodermal activity and digital blood flow after the startle stimuli were investigated in similar analyses. Although the normality assumption was not met for some of the variables included in these analyses, analysis of variance generally is robust to such violations and, unlike non-parametric approaches, permits investigation of interaction between factors. Individual differences in the intensity and asymmetry of startle-hyperalgesia (from before to after the tone) were investigated in relation to age, pain intensity, pain duration, ipsilateral forehead hyperalgesia, hyperalgesia in the symptomatic limb and auditory discomfort with Spearman’s rank-order correlation coefficient. A similar analysis was conducted to
determine associations between auditory discomfort and age, pain intensity, pain duration, forehead hyperalgesia, ipsilateral forehead hyperalgesia and hyperalgesia in the affected limb. Data is presented as the mean ± standard error of the mean.

**Results**

*Sensory disturbances in the symptomatic limb*

PPTs were lower in the symptomatic limb than the healthy limb (464 ± 105 g versus 1257 ± 105 g) [Wilcoxon’s Z = -4.23, p < 0.001], consistent with hyperalgesia to pressure-pain. Similarly, sharpness ratings generally were greater in the symptomatic limb (mean rating 4.36 ± 0.63) than the healthy limb (mean rating 2.59 ± 0.41) [Wilcoxon’s Z = -2.29, p < 0.05], indicating punctate hyperalgesia.

*Sensory disturbances in the forehead*

In the group as a whole, PPTs in the forehead were significantly lower on the CRPS-affected side than contralaterally (551 ± 59 g versus 654 ± 58 g) [Wilcoxon’s Z = -1.97, p < 0.05]. Sharpness sensations to the bristle did not differ between the ipsilateral and contralateral sides of the forehead in the group as a whole [mean ratings 4.04 ± 0.53 and 3.02 ± 0.46 respectively, Wilcoxon’s Z = -1.61, not significant]. However, asymmetry of sharpness sensations in the limbs was associated with asymmetry of sharpness and pressure-pain sensations in the forehead (Table 2), consistent with a spread of sensory disturbances from the CRPS-affected limb to the ipsilateral forehead.
**Startle response**

Auditory discomfort was greater when the tone was presented on the CRPS-affected side than contralaterally [mean discomfort 5.80 ± 0.51 versus 4.96 ± 0.48, Wilcoxon’s Z = 2.42, p < 0.05]. Most (21) patients reported that limb pain increased after the startle stimuli; however, six patients reported no change and one other reported that limb pain decreased (Fig. 1). In the startle-responsive group, limb pain increased immediately and remained elevated for at least 30 s [main effect for Time F(2.46,49.25) = 9.66, p < 0.001]. The immediate increase was most pronounced when the tone was presented on the CRPS-affected side [mean increase 1.23 ± 0.21 to ipsilateral stimuli versus 0.68 ± 0.16 to contralateral stimuli, Wilcoxon’s Z = -3.16, p < 0.01] and pain remained greater during ipsilateral than contralateral startle for the entire 30 s post startle [Time x Startle Side interaction F(3.83,76.59) = 5.58, p < 0.001].

Differences between startle-responders and non-responders were investigated with Wilcoxon’s test and Fisher’s exact test for small samples (Table 3). Startle-responders were characterized by greater generalized forehead hyperalgesia to pressure-pain and sharpness and greater ipsilateral forehead hyperalgesia to sharpness, greater pain in the CRPS-affected limb and greater auditory discomfort from the tone. During their initial physical examination, only one of the six non-responders (17%) reported that limb pain increased when they were anxious, angry or distressed or after being startled or frightened. In contrast, 81% of the startle-responders reported that such stimuli aggravated their pain. The number of patients on medication was similar in the two groups (Table 3).

Greater hyperalgesia to startle on the CRPS-affected side was associated with greater auditory discomfort on the CRPS-affected side (Table 4). In addition, greater auditory discomfort on the affected side was associated with greater hyperalgesia to pressure on the ipsilateral side of the forehead (Table 5), and greater auditory discomfort, in
general, was associated with greater limb pain and with greater bilateral punctate hyperalgesia in the forehead (Table 5).

Sweating and blood flow

In the 11 patients included in this part of the study, electrodermal activity (sweating) increased to the same extent in both limbs after the startle stimuli, irrespective of the side stimulated (mean increase 3.94 ± 1.0 µS). Eight of the 11 patients reported increased pain to startle, whereas three patients were startle non-responders. When the three non-responsive patients were removed from the analysis, the electrodermal response was greater in the healthy than symptomatic limb, irrespective of whether the tone was presented on the CRPS-affected side or contralaterally [mean increase 4.8 ± 1.7 µS versus 3.0 ± 1.1 µS, main effect for Limb F(1,7) = 6.22, p < 0.05].

Digital blood flow did not change in either limb after startle in either ear (mean decrease 1 ± 8%). These results did not change after excluding the non-responders.

Discussion

Auditory startle stimuli evoked greater increases in limb pain and auditory discomfort when presented on the CRPS-affected side than when presented contralaterally. As startle stimuli inhibit nociceptive sensations in healthy controls [13], these findings suggest that mechanisms that normally inhibit activity in nociceptive networks are compromised in patients with CRPS. They further imply that processing of signals from multiple sensory modalities is disrupted hemilaterally.

In a recent study, pain ratings to repetitive noxious electrical stimulation of the hands decreased more slowly in CRPS patients than controls (consistent with impaired
inhibitory pain modulation), whereas the area of pinprick hyperalgesia increased to a greater extent in the CRPS-affected limb than the contralateral healthy limb (consistent with an ipsilateral enhancement of facilitatory pain modulation) [46]. Such disturbances probably mediated allodynia and mechanical hyperalgesia in the CRPS-affected limb of our patients, and might also have contributed to sensory disturbances that spread beyond the CRPS-affected limb to the forehead.

Such disturbances might also have mediated the hyperalgesia and auditory discomfort evoked by startle stimuli. In a study of 40 patients with CRPS-related dystonia, 15 (38%) reported hyperacusis to bilateral ear stimulation [10]. The hyperacusis was attributed to central sensitization as it was associated with allodynia and/or hyperalgesia in the symptomatic limb. Although this finding was not replicated in our study, auditory discomfort was associated with greater limb pain and with hyperalgesia in the forehead. Perhaps a lack of inhibitory control promotes uncontrolled sensitization or unmasks facilitatory mechanisms, particularly in pathways subserving the CRPS-affected limb [18; 25; 36; 40; 45; 53].

The source of the auditory-nociceptive interaction in CRPS is uncertain. One possibility is the cochlear nucleus (CN), which is the first link in the neural pathway underlying the acoustic startle response [56] and the lone site in the central auditory system that exclusively receives unilateral input from the adjacent ipsilateral ear [12]. Importantly, supraspinal sites involved in the descending control of pain such as the locus coeruleus (LC) [17; 31; 43] and the raphe nuclei [49] project to the CN. The LC is active during acoustic startle [20], possibly via dorsal CN activation of the lateral paragigantocellular nucleus in the reticular formation which provides excitatory input to the LC [26]. Alternatively, output from the amygdala and periaqueductal gray during startle [58] might activate the LC. The LC plays a dual role in neuronal modulation, producing both
facilitation and inhibition in the dorsal horn and the CN via $\alpha_1$-adrenoceptors and $\alpha_2$-
adrenoceptors respectively [8; 17; 22; 24; 31; 43]. Thus, a shift in the inhibitory-facilitatory
balance of LC control might facilitate nociceptive traffic in the dorsal horn and auditory
signals in the CN.

The LC is active in the ipsilateral, but not the contralateral dorsal horn during
unilateral hindpaw inflammation [50-52], thus providing a possible neuroanatomical
substrate for the lateralized deficits in pain control observed in our patients. Whereas spinal
input to the thalamus is contralateral, spinobulbar projections are bilateral [2; 9]. Thus,
ipsilateral spinobulbar nociceptive projections from the dorsal horn and trigeminal nuclei
could intersect with CN and LC pathways in the brainstem and midbrain, potentially
establishing an ipsilateral facilitatory loop. Serotonergic projections from raphe nuclei also
have both excitatory and inhibitory effects on CN [16] and dorsal horn neurons [59] and
could account for a more generalized facilitation of somatosensory and auditory activity
during startle. This could also explain the association between migraine and CRPS [11],
which share symptoms such as hyperalgesia and phonophobia [34; 38; 55].

Another potential mechanism underlying hyperacusis in CRPS includes
convergence of auditory input onto sensitized thalamic nuclei [10]. Reports of auditory
discomfort to auditory stimulation in CRPS in the present and a previous study [10] may
also indicate involvement of the limbic system [10], as startle stimuli generally evoke
momentary fright. It is worth noting that both noradrenergic LC and serotonergic raphe
nuclei innervate the thalamus [1; 57] and the limbic system [19; 23], and could thus up- or
down-regulate nociceptive signals and emotional responses in parallel. Finally, cochlear
disturbances might contribute to loudness recruitment on the CRPS-affected side. Although
possible, this seems unlikely as pure tone audiogram thresholds and speech reception
thresholds were within the normal range in CRPS patients with hyperacusis in a previous
study [10]. Furthermore, none of the patients in the present study reported a history of hearing problems.

The nociceptive effect of startle may also have a peripheral component, mediated by adrenergic excitation of sensitized nociceptors [14]. Although sweating increased in both limbs to startle, the response was greater in the contralateral healthy limb than the symptomatic limb implying sudomotor dysfunction in the CRPS-affected limb [5; 6; 15; 27; 30; 47; 54]. As increased sweating in the symptomatic limb appears to be associated with adrenergic supersensitivity [7], the lesser degree of sweating in this limb does not support peripheral adrenergic mediation of startle-hyperalgesia. Moreover, vasoconstrictor responses to startle (normally mediated by adrenergic vasomotor neurons) were minimal. Visual inspection of the response curves indicated that vasoconstriction preceded the startle stimulus in most cases, perhaps due to the warning given prior to startle. Attenuated vasoconstrictor reflexes in the limbs of CRPS patients, particularly on the symptomatic side, may also reflect a central disturbance in sympathetic vasomotor control [3; 4; 32; 33; 44].

Forehead hyperalgesia, auditory discomfort and pain in the affected limb were greater in the 21 patients with increased pain during startle than in six non-responsive patients. These findings suggest an association between startle-hyperalgesia and other sources of pain in CRPS. Nevertheless, dynamic allodynia, which is thought to reflect central sensitization, was detected in the symptomatic limb of all but one of the six non-responsive patients. Whether failure of pain modulation mechanisms differentiates startle-responders from non-responders requires further investigation.

A potential limitation of this study is that limb pain may have increased during startle due to movement. However, this does not account for greater increases in pain and auditory discomfort to startle stimuli on the CRPS-affected side. Similarly, pain
medication, although a potential influence, would be expected to suppress rather than enhance responses to startle. A further limitation is that the assessment technique relied on patient-reported pain ratings, which are sensitive to subjective influences. However, this is unlikely to have played a major role as patients were unaware of the purpose of the study.

In conclusion, our findings suggest that modulation of activity in nociceptive networks is compromised in the majority of patients with CRPS, predominantly in central pathways that serve the CRPS-affected side of the body. Activity in pathways that converge upon this sensitized system (e.g., from the somatosensory supply of ipsilateral body sites, the cochlear nucleus, or locus coeruleus) may intensify nociceptive sensations in the CRPS-affected limb and evoke discomfort to stimulation on the CRPS-affected side of the body.
Acknowledgements

The authors wish to thank Dr Kenneth Maguire, Perth Orthopaedic and Sports Medicine Centre, Western Australia and Dr John Salmon, Besthesda Hospital, Perth, Western Australia, for assisting with the recruitment of patients for the study.
References


[58] Zhao Z, Davis M. Fear-potentiated startle in rats is mediated by neurons in the deep layers of the superior colliculus/deep mesencephalic nucleus of the rostral midbrain through the glutamate non-NMDA receptors. J Neurosci 2004;24:10326-34.

Table 1

Sensory, vasomotor/sudomotor and motor/trophic disturbances in CRPS patients

<table>
<thead>
<tr>
<th>Limb</th>
<th>Pain duration (months)</th>
<th>Sensory</th>
<th>Vasomotor/sudomotor</th>
<th>Motor/trophic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hyperalgesia</td>
<td>Allodynia</td>
<td>Temp. sensation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allodynia</td>
<td>Cold</td>
<td>Flushed/cyanotic</td>
</tr>
<tr>
<td>1. F, 59</td>
<td>RU</td>
<td>28</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>3. F, 52</td>
<td>RL</td>
<td>139</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>4. M, 46</td>
<td>LL</td>
<td>24</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>6. M, 21</td>
<td>RL</td>
<td>16</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>9. F, 45</td>
<td>LU</td>
<td>36</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>11. M, 48</td>
<td>LU</td>
<td>24</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>12. F, 35</td>
<td>RU</td>
<td>8</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>13. F, 39</td>
<td>RU</td>
<td>74.5</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>19. F, 41</td>
<td>LU</td>
<td>127</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>20. F, 36</td>
<td>LL</td>
<td>11</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>21. F, 52</td>
<td>RL</td>
<td>202</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>22. F, 49</td>
<td>RL</td>
<td>47</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>23. F, 33</td>
<td>RU</td>
<td>81</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>No.</td>
<td>Gender</td>
<td>Site</td>
<td>Age</td>
<td>Pain</td>
</tr>
<tr>
<td>-----</td>
<td>--------</td>
<td>------</td>
<td>-----</td>
<td>------</td>
</tr>
<tr>
<td>24. F, 15</td>
<td>RL</td>
<td>13</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>25. F, 22</td>
<td>RL</td>
<td>18</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>26. F, 43</td>
<td>RU</td>
<td>4.5</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>27. F, 44</td>
<td>LU</td>
<td>55</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>31. F, 59</td>
<td>LL</td>
<td>86</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>32. F, 49</td>
<td>LL</td>
<td>107</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>33. F, 46</td>
<td>LU</td>
<td>46</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
<tr>
<td>34. F, 53</td>
<td>RL</td>
<td>5.5</td>
<td>hyperalgesia</td>
<td>allodynia</td>
</tr>
</tbody>
</table>

Non-responders

<table>
<thead>
<tr>
<th>No.</th>
<th>Gender</th>
<th>Site</th>
<th>Age</th>
<th>Pain</th>
<th>Hyperalgesia</th>
<th>Allodynia</th>
<th>Temperature</th>
<th>Coloration</th>
<th>Other Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. F, 36</td>
<td>RU</td>
<td>35</td>
<td>hyperalgesia</td>
<td>allodynia</td>
<td>hot/cold</td>
<td></td>
<td>sweats</td>
<td>intention</td>
<td>more</td>
<td>fast</td>
</tr>
<tr>
<td>7. F, 29</td>
<td>RL</td>
<td>27</td>
<td>hyperalgesia</td>
<td>allodynia</td>
<td>cold</td>
<td>flushed/cyanotic</td>
<td></td>
<td>resting</td>
<td></td>
<td>yellow</td>
</tr>
<tr>
<td>10. M, 50</td>
<td>RU</td>
<td>230</td>
<td>hyperalgesia</td>
<td>allodynia</td>
<td>hot/cold</td>
<td>flushed</td>
<td>sweats</td>
<td>resting</td>
<td>less</td>
<td>dystrophy</td>
</tr>
<tr>
<td>14. F, 20</td>
<td>LU</td>
<td>2</td>
<td>hyperalgesia</td>
<td>allodynia</td>
<td>hot/cold</td>
<td>flushed</td>
<td>sweats</td>
<td>resting</td>
<td>dystonia</td>
<td></td>
</tr>
<tr>
<td>28. M, 48</td>
<td>RL</td>
<td>90</td>
<td>hyperalgesia</td>
<td>allodynia</td>
<td>cold</td>
<td>flushed/cyanotic</td>
<td>sweats</td>
<td>resting</td>
<td>less</td>
<td>scaly</td>
</tr>
<tr>
<td>30. F, 55</td>
<td>RL</td>
<td>96</td>
<td>hyperalgesia</td>
<td>allodynia</td>
<td>hot</td>
<td>cyanotic</td>
<td>sweats</td>
<td></td>
<td>sensitive</td>
<td>glossy/scaly</td>
</tr>
</tbody>
</table>

Pain-reduction patient

<table>
<thead>
<tr>
<th>No.</th>
<th>Gender</th>
<th>Site</th>
<th>Age</th>
<th>Pain</th>
<th>Hyperalgesia</th>
<th>Allodynia</th>
<th>Temperature</th>
<th>Coloration</th>
<th>Other Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>29. F, 34</td>
<td>RU</td>
<td>106</td>
<td>hyperalgesia</td>
<td>allodynia</td>
<td>cold</td>
<td>flushed/cyanotic</td>
<td></td>
<td>intention</td>
<td></td>
<td>scaly</td>
</tr>
</tbody>
</table>

Symptom history as reported by patients. Signs of disturbances noted during the physical examination are *italicized in bold*. A blank space indicates a
lack of that particular symptom. *Limb* LU, left upper extremity; RU, right upper extremity; LL, left lower extremity; RL, right lower extremity. *Sensory disturbances* reported by patients included hyperalgesia, allodynia and numbness. Numbness was reported by all but seven patients (Nos. 4, 10, 23, 24, 25, 32, 34). The extent of hyperalgesia (to punctate stimulation) and allodynia (to brushing) in the symptomatic and the contralateral healthy limb was assessed during the physical examination. Sharpness was rated in response to a single application of a firm nylon bristle (Filament 17, Senselab von Frey Aesthesiometer, Somedic Sales AB, Sweden) on a scale from 0 (not sharp) to 10 (stabbing). The bristle was applied with sufficient force to bend it for 1 s. Punctate hyperalgesia was defined as a sharpness rating at least 2 higher on a 0-10 scale in the affected than the unaffected limb. Patients rated the sensation to 3-4 light backwards-forwards strokes with a small brush as a normal or abnormal sensation. Descriptions of the brushing as uncomfortable, scratching or painful were regarded as allodynia. Three patients reported a numb sensation to the brushing (Nos. 9, 11, 24). *Vasomotor and sudomotor disturbances* reported by patients were asymmetrical temperature sensations, dyschromia and hyperhidrosis. Limb temperature was also obtained from both the symptomatic and the equivalent healthy limb. This was done after the patient had rested quietly for at least 20 minutes in a room maintained at 20 ± 2°C. The temperature of the first phalanx of each toe was determined in lower limb CRPS patients, whilst the equivalent was obtained in the fingers of patients with upper limb pain, using an infrared skin thermometer (Tempett IR Thermometer, Somedic Sales AB, Sweden). A temperature difference greater than 1°C was regarded as asymmetrical (e.g., a hot or cold limb) and is *italicized in bold*. Swelling was reported by all patients except one (No. 10). *A decreased range of movement* was observed and reported by all but two patients (Nos. 23 and 28). Other *motor disturbances* reported by patients included weakness (all but patient no. 34), tremor and dystonia. *Trophic changes* (hair, nails, skin) varied greatly between patients.
Table 2

Association (Spearman’s rank-order correlation coefficient) between sensory disturbances in the affected limb and asymmetry of sensations in the forehead

<table>
<thead>
<tr>
<th>Ipsilateral side of the forehead (compared with the contralateral side)</th>
<th>Sensations in the affected limb (compared with the unaffected limb)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pressure hyperalgesia</td>
</tr>
<tr>
<td>Pressure hyperalgesia</td>
<td>0.18</td>
</tr>
<tr>
<td>Punctate hyperalgesia</td>
<td>-0.04</td>
</tr>
</tbody>
</table>

** p < 0.01; *** p < 0.001
Table 3

Demographic and sensory characteristics in startle-responders and non-responders

<table>
<thead>
<tr>
<th></th>
<th>Startle-responders (N = 21)</th>
<th>Non-responders (N = 6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>86%</td>
<td>67%</td>
<td>0.30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.24 ± 2.59</td>
<td>39.67 ± 5.55</td>
<td>0.77</td>
</tr>
<tr>
<td>Pain intensity (0-10)</td>
<td>5.38 ± 0.37</td>
<td>3.10 ± 0.89</td>
<td>0.02</td>
</tr>
<tr>
<td>Pain duration (months)</td>
<td>49.17 ± 8.99</td>
<td>80 ± 33.55</td>
<td>0.52</td>
</tr>
<tr>
<td>Forehead hyperalgesia (overall mean)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPT (g)</td>
<td>530 ± 40</td>
<td>853 ± 183</td>
<td>0.06</td>
</tr>
<tr>
<td>Sharpness (0-10)</td>
<td>3.86 ± 0.48</td>
<td>2.08 ± 0.40</td>
<td>0.07</td>
</tr>
<tr>
<td>Ipsilateral forehead hyperalgesia (ipsilateral vs. contralateral forehead)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPT (g)</td>
<td>142 ± 54</td>
<td>-40 ± 68</td>
<td>0.39</td>
</tr>
<tr>
<td>Sharpness (0-10)</td>
<td>1.76 ± 0.69</td>
<td>-0.50 ± 0.22</td>
<td>0.04</td>
</tr>
<tr>
<td>Hyperalgesia in the symptomatic limb (symptomatic vs. contralateral limb)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPT (g)</td>
<td>-843 ± 116</td>
<td>-717 ± 394</td>
<td>0.84</td>
</tr>
<tr>
<td>Sharpness (0-10)</td>
<td>2.24 ± 0.79</td>
<td>1 ± 1.51</td>
<td>0.21</td>
</tr>
<tr>
<td>Auditory discomfort (0-10)</td>
<td>5.87 ± 0.50</td>
<td>3.44 ± 1.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Greater ipsilateral auditory discomfort (0-10) (ipsilateral vs. contralateral startle)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>71%</td>
<td>100%</td>
<td>0.18</td>
</tr>
<tr>
<td>Pain aggravation history (when anxious, angry, upset, startled or frightened)</td>
<td>81%</td>
<td>17%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*aFisher’s exact test. bWilcoxon test.*
Table 4

Association (Spearman’s rank-order correlation coefficient) between greater ipsilateral startle hyperalgesia (compared with contralateral startle hyperalgesia) and age, limb pain (intensity, duration), asymmetry of sensations in the forehead, asymmetry of sensations in the limbs, and auditory discomfort (mean, asymmetry)

<table>
<thead>
<tr>
<th></th>
<th>Ipsilateral forehead hyperalgesia (ipsilateral vs. contralateral forehead)</th>
<th>Hyperalgesia in the affected limb (symptomatic vs. contralateral limb)</th>
<th>Auditory discomfort (ipsilateral vs. contralateral startle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Pain, Pain, Pain intensity, duration, PPT, Sharpness, PPT, Sharpness, Mean, Asymmetry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Startle hyperalgesia asymmetry</td>
<td>0.08, 0.34, 0.22, -0.33, 0.18, -0.07, 0.08, 0.52**, 0.68***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** p < 0.01; *** p < 0.001
Table 5

Associations (Spearman’s rank-order correlation coefficient) between auditory discomfort (mean, asymmetry) and age, limb pain (intensity, duration), hyperalgesia in the forehead and hyperalgesia in the affected limb

<table>
<thead>
<tr>
<th>Age</th>
<th>Pain intensity</th>
<th>Pain duration</th>
<th>Forehead hyperalgesia (overall mean)</th>
<th>Ipsilateral forehead hyperalgesia (ipsilateral vs. contralateral forehead)</th>
<th>Hyperalgesia in the affected limb (symptomatic vs. contralateral limb)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PPT</td>
<td>Sharpness</td>
<td>PPT</td>
</tr>
<tr>
<td>Mean auditory discomfort</td>
<td>0.05</td>
<td>0.47*</td>
<td>0.15</td>
<td>-0.01</td>
<td>0.68***</td>
</tr>
<tr>
<td>Auditory discomfort asymmetry (ipsilateral vs. contralateral startle)</td>
<td>0.2</td>
<td>0.07</td>
<td>0.36</td>
<td>-0.31</td>
<td>0.16</td>
</tr>
</tbody>
</table>

* p < 0.05; *** p < 0.001
Fig. 1. Pain ratings before and for 30 s after startle in the ear ipsilateral to the affected limb (filled circles) and the contralateral ear (clear circles) for the 21 startle-responders (A), the 6 non-responders (B) and the patient with a reduction in pain to startle (C). The pain increase was greater during ipsilateral than contralateral startle in startle-responders (# \( p < 0.01 \)) and the pain following ipsilateral startle remained greater than the pain following contralateral startle for the entire 30 s post startle period (*** \( p < 0.001 \)). Note that the y-axes differ in the three graphs. Error bars indicate standard errors and the arrow represents the loud tone.
CHAPTER 10

FAILURE OF INHIBITORY PAIN MODULATION TO
NOXIOUS STIMULATION OF THE SYMPTOMATIC LIMB,
BUT NOT THE HEALTHY LIMB, IN COMPLEX
REGIONAL PAIN SYNDROME

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Pages: 31
Tables: 1
Figures: 4

Key words: complex regional pain syndrome; cold pressor; diffuse noxious inhibitory controls; laterality; locus coeruleus
Abstract

Complex regional pain syndrome (CRPS) is characterized by sensory disturbances that spread in a hemilateral distribution on the affected side of the body, and by contralateral changes in the sensory and motor cortices. In addition, central inhibitory pain control is disrupted. The aim of this study was to determine whether the dysfunction in inhibitory control is limited to the affected side of the body. In 22 CRPS patients, sharpness sensations and pressure-pain thresholds were assessed on each side of the forehead and in the symptomatic and contralateral healthy limb before and after immersion of each limb in painfully-cold water for one minute (the cold pressor task). Immersion of the healthy limb produced bilateral forehead analgesia to pressure-pain and a reduction in clinical pain in the CRPS-affected limb. However, sensitivity to pressure-pain increased in the forehead after immersion of the symptomatic limb. The findings suggest that nociceptive stimulation of the CRPS-affected limb fails to evoke central inhibitory pain control processes. Disruption of inhibitory pain modulation may contribute to uncontrolled sensitization to incoming stimuli from the ipsilateral side of the body, and may account for hemilateral sensory changes ipsilateral to the affected limb in CRPS.
Introduction

Noxious stimuli activate central facilitatory and inhibitory mechanisms that not only modify perception of the noxious stimulus but which also modify perception of pain more generally. For instance, diffuse noxious inhibitory controls (DNIC), which emanate from the caudal medulla, produce widespread inhibition of wide dynamic range neurons in the dorsal horn and trigeminal nucleus caudalis through a counter-stimulation process [6; 14; 27]. Likewise, stress-induced analgesia (SIA), mediated by opioid and non-opioid mechanisms [35; 48], is thought to exert widespread inhibition of pain.

Complex regional pain syndrome (CRPS) is characterised by limb pain and motor, autonomic and sensory disturbances [3; 19; 55] which often spread to include other parts of the body particularly on the ipsilateral side [16; 43; 44; 49]. Pressure-pain thresholds, for instance, were found to be lower in the forehead ipsilateral to the affected limb than in the contralateral forehead, and hyperalgesia to punctuate stimulation in the ipsilateral forehead was associated with punctuate hyperalgesia in the affected limb [16]. A hemilateral loss of sensation to tactile stimuli has also been reported in CRPS [43; 44; 49]. Interestingly, CRPS pain is associated with hyperexcitability in the somatosensory and motor cortices that process input from and output to the symptomatic limb [17; 24; 30; 45], consistent with lateralised disturbances in neuronal pathways that subserve the pain.

CRPS pain increases in response to forehead cooling and to startle with a loud tone [15]. In contrast, capsaicin-induced thermal hyperalgesia decreases during such stimuli in healthy volunteers, thus implying that a disruption of central inhibitory pain control may contribute to the syndrome [15]. To our knowledge, only Seifert and colleagues [46] have assessed whether inhibitory pain control differs between the affected and unaffected limbs.
in patients with CRPS. They reported reduced inhibitory control (as exemplified by a slower decline in pain ratings) compared to controls during repetitive noxious electrical stimulation of both the CRPS-affected and unaffected limb. In addition, facilitation (indicated by a greater area of pinprick hyperalgesia) was enhanced in the affected limb.

The aim of our study was to further investigate the apparent lack of inhibitory control in CRPS, in particular in terms of laterality. More specifically, we assessed the influence of unilateral noxious-cold stimulation of a limb on sensory disturbances in the limbs and forehead of patients with CRPS. We hypothesized that noxious stimulation of the healthy limb would evoke analgesia in the forehead (consistent with inhibitory pain control). In addition, we hypothesized that sensory disturbances in the forehead would persist or intensify during noxious stimulation of the CRPS-affected limb, due to failure of inhibitory pain control on this side of the body.

Method

Subjects

Twenty-two patients (6 males) with a mean age of 40.05 ± 2.69 years (range 15-59) who met the International Association for the Study of Pain criteria [34] for CRPS I (21 patients) or CRPS II (1 patient) participated in the study (Table 1). All but 1 patient met the more stringent criteria by Harden and colleagues [20]. The lower limb was affected in 11 patients and the upper limb in the remaining 11 patients. The median duration of CRPS pain was 5.2 years (range 2 months – 19.2 years). Sixteen patients were receiving treatment with analgesics, anticonvulsants and/or anti-depressants and 6 other patients were medication-free. Due to ethical and practical concerns relating to discontinuation of
medication, patients were not asked to abstain from routine medication during the trial. During an initial physical examination, sensory, vasomotor/sudomotor and motor/trophic disturbances were reported by patients and noted by an experienced medically-trained pain specialist. In addition, psychophysical assessments were performed to determine the presence of sensory disturbances (punctate hyperalgesia and dynamic allodynia) in the affected limb (Table 1). The procedures were approved by the Murdoch University Human Research Ethics Committee and informed consent was obtained from each participant.

Procedures

Procedures were performed in a laboratory maintained at 20 ± 2°C.

Sensory assessments. Sensitivity to blunt pressure and sharpness sensations to a firm bristle were assessed on each side of the forehead and on the CRPS-affected hand or foot and on the contralateral healthy limb. A spring-loaded algometer with a rounded tip (1 cm diameter) was used to apply pressure in increments of 200 g on each limb and in increments of 80 g on each side of the forehead [18; 25]. This was done to a maximum of 2.3 kg or until the participant felt pain. Sharpness was rated on a scale from 0 (not sharp) to 10 (stabbing) at each site in response to a single application with a firm nylon bristle (Filament 17, Senselab von Frey Aesthesiometer, Somedic Sales AB, Sweden) [18; 25]. Enough force was applied to bend the bristle for 1 second.

Cold Pressor. The cold pressor task involved immersion of the limb in a 2 ± 1°C cold water bath for 1 min [25]. If the participant could not tolerate the 2°C temperature,
10°C was used. An aquarium pump was used to circulate the water to avoid the build-up of heat around the limb. The patient reported the pain induced by the cold pressor verbally from 0 (no pain) to 10 (extremely severe pain) and also rated the level of distress caused by the immersion on a scale from 0 (no distress) to 10 (extremely severe distress). These scales were also used to rate pain and associated distress in the symptomatic limb.

**Trial.** The cold pressor task was performed in both the CRPS-affected limb and the healthy limb. Sensory assessments were conducted before and after each cold pressor, and were repeated at 2 min intervals for 12 min after each cold pressor [25]. Pain and distress ratings were also obtained at these times as well as 30 s into the immersions. In half the patients, the CRPS-affected limb was immersed first followed by the contralateral healthy limb. The reverse order applied to the remaining participants. At least 15 min elapsed between the two cold pressor trials.

**Statistical analysis.** Some of the score distributions did not fit a normal bell-shaped curve; thus, where appropriate, nonparametric statistical analyses were employed. As analysis of variance generally is robust to violations of normality, repeated measures analysis of variance was used to assess changes in pain and distress ratings to immersion of the healthy limb versus the CRPS-affected limb. Changes from baseline at each time point were investigated with simple contrasts. Repeated measures analysis of variance was also employed to detect any differential influences of immersion of the healthy limb versus the CRPS-affected limb on pressure-pain and sharpness sensations in the forehead (ipsilateral versus contralateral to the CRPS-affected limb). Changes in pressure-pain and sharpness sensations in the healthy and the CRPS-affected limb after the cold pressor task were
assessed in a similar analysis of variance. The Huynh-Feldt epsilon was used to correct for violations of sphericity. Changes in clinical pain to immersion of the healthy limb were investigated in a one-way repeated measures analysis of variance. Wilcoxon’s matched pairs signed-ranks tests or analysis of variance were used, as appropriate, for post hoc analyses. Data is presented as the mean ± standard error of the mean.

Results

Limb pain induced by cold water immersion

Patients described their CRPS-affected limb as being moderately painful (mean rating 5.11 ± 0.61 on a 0-10 scale) and distress from the pain averaged slight to moderate (mean rating 3.49 ± 0.74 on a 0-10 scale). Only seven patients tolerated a water temperature of 2°C for their CRPS-affected limb while all but three patients tolerated this temperature for their contralateral healthy limb. Nonetheless, pain in the CRPS-affected limb during immersion of this limb (mean rating 8.10 ± 0.52) was similar to the pain in the healthy limb during healthy limb immersion (mean rating 7.91 ± 0.56) [Wilcoxon’s Z = -0.41, p = 0.681]. Pain in the healthy limb decreased at a faster rate upon removal from the water [Time x Limb interaction F(2.92,61.28) = 9.98, p = 0.000] (Fig. 1A); straight after the cold pressor, the pain was significantly lower in the healthy limb than it was after the cold pressor in the CRPS-affected limb [Wilcoxon’s Z = -2.89, p = 0.004]. Distress ratings during immersion of the CRPS-affected limb (mean rating 6.21 ± 0.74) were similar to distress ratings during immersion of the healthy limb (mean rating 6.09 ± 0.78) [Wilcoxon’s Z = -0.51, p = 0.608]. However, distress decreased more rapidly following withdrawal of the healthy limb than following withdrawal of the CRPS-affected limb [Time
x Limb interaction $\text{F}(3.52,73.98) = 2.93, p = 0.032$] (Fig. 1B). A difference in distress levels emerged immediately after the CP [Wilcoxon’s $Z = -2.42, p = 0.016$].

**Effect of the cold pressor task on sensitivity to pain in the forehead**

Before the limb immersions, pressure-pain thresholds generally were lower on the forehead ipsilateral to the CRPS-affected limb ($M = 529 \pm 55$ g) than on the contralateral forehead ($M = 593 \pm 55$ g) [Wilcoxon’s $Z = -1.86, p = 0.063$], consistent with ipsilateral forehead hyperalgesia. This persisted during the limb immersions (Fig. 2) [main effect for Forehead $\text{F}(1,21) = 9.04, p = 0.007$]. Bilateral changes in forehead sensations to pressure-pain, rather than unilateral changes, were detected during the limb immersions (Fig. 2A and 2B). These changes differed between immersion of the healthy limb and the CRPS-affected limb [Time x Immersion (CRPS-affected Limb, Healthy Limb) interaction $\text{F}(4.12, 86.57) = 2.87, p = 0.027$]. During immersion of the healthy limb, forehead sensitivity to pressure-pain reached its highest point 2 min after the cold pressor [$p = 0.07$ compared with baseline], but then gradually decreased to a minimum 10 min after the cold pressor [$p = 0.06$ compared with baseline] [main effect for Time (immersion healthy limb) $\text{F}(4.95,103.87) = 3.52, p = 0.006$]. In contrast, immersion of the CRPS-affected limb resulted in an immediate increase in forehead sensitivity [$p = 0.016$ compared with baseline] which persisted for the remainder of the forehead assessments [main effect for Time (immersion CRPS-affected limb) $\text{F}(3.35,70.31) = 4.28, p = 0.006$].

Sharpness sensations were symmetrical in the forehead ipsilateral (mean rating $3.84 \pm 0.62$) and contralateral (mean rating $2.99 \pm 0.58$) to the CRPS-affected limb before the limb immersions [Wilcoxon’s $Z = -1.42, p = 0.155$]. This did not change during immersion of either limb (Fig. 2) [main effect for Forehead $\text{F}(1,21) = 1.15, p = 0.295$]. In fact,
sharpness sensations in general remained unchanged throughout both limb immersions (Fig. 2C and 2D).

**Effect of the cold pressor task on sensitivity to pain in the limbs**

Pain in the CRPS-affected limb decreased during immersion of the healthy limb \([p = 0.027\) compared with baseline\] but returned to pre-immersion levels immediately upon removal of the healthy limb from the water (Fig. 3) [main effect for Time F(2.37,49.68) = 2.65, \(p = 0.072\)].

Before the limb immersions, pressure-pain thresholds were lower in the affected limb \((M = 520 \pm 135 \text{ g})\) than the contralateral limb \((M = 1214 \pm 135 \text{ g})\) [Wilcoxon’s \(Z = -3.68, p = 0.000\)] indicating pressure hyperalgesia in the CRPS-affected limb. This difference in pressure sensitivity between the two limbs persisted during the limb immersions (Fig. 4) [main effect for Limb (CRPS-affected Limb, Healthy Limb) F(1,21) = 34.23, \(p = 0.000\)]. Immersion of the healthy limb did not influence pressure hyperalgesia in the CRPS-affected limb (as measured after healthy limb immersion) (Fig. 4A), and immersion of the CRPS-affected limb similarly did not influence sensations to pressure-pain in the contralateral healthy limb (Fig. 4B).

Sharpness sensations were similar in the CRPS-affected limb (mean rating 3.49 \(\pm 0.65\)) and the contralateral limb (mean rating 2.55 \(\pm 0.46\)) before the limb immersions [Wilcoxon’s \(Z = -1.36, p = 0.173\)] and throughout the trials (Fig. 4). Sharpness sensations both in the symptomatic limb and the healthy limb were unaffected by the limb immersions (Fig. 4C and 4D).
Discussion

The main finding of this study was an analgesic effect of immersion of the healthy limb on general forehead sensitivity to pressure-pain and on pain in the CRPS-affected limb. In contrast, no analgesic effects were observed when the CRPS-affected limb was immersed. In fact, forehead sensitivity to pressure-pain increased. Together, these findings suggest that supraspinal inhibitory pain control processes remain intact, although slightly impaired, in CRPS. However, nociceptive afferent input from the CRPS-affected limb either fails to evoke these inhibitory processes or simultaneously evokes a pain facilitatory mechanism that masks inhibitory influences.

When triggered by nociceptive stimulation, diffuse noxious inhibitory controls (DNIC) normally inhibit the activity of trigeminal [14; 37] and dorsal horn wide dynamic range neurons [27; 36] in a counter-stimulation process. The neurons that mediate DNIC originate in the subnucleus reticularis dorsalis of the caudal medulla, and operate in a supraspinal loop [5; 6; 13; 42; 56]. The diffuse inhibitory effects observed during painfully-cold stimulation in healthy volunteers are largely attributed to DNIC [2; 15; 25; 26; 29; 39; 57; 58; 60].

The patients in the present study experienced severe pain in their CRPS-affected limb during cold water immersion which, under normal circumstances, would be expected to reduce pain sensitivity at remote sites in the body [25]. Nevertheless, stimulation of the CRPS-affected limb failed to induce inhibitory effects. As the 10°C cold water immersion of the CRPS-affected limb was as painful as the 2°C cold water immersion of the healthy limb, the temperature of the water is unlikely to account for the absence of DNIC. In contrast to the present findings, DNIC effects induced by stimulating the affected limb were
found to be enhanced in animals with monoarthritis, polyarthrits or a peripheral mononeuropathy [4; 9; 11; 12; 28]. DNIC effects were also observed during normally non-painful stimulation of an area of static allodynia in patients with peripheral nerve injury [7].

The findings may indicate dysfunction in neuronal pathways or supraspinal sites subserving DNIC from the CRPS limb. In patients with unilateral lesions of the retro-olivary portion of the medulla (Wallenberg’s syndrome), no DNIC effect was observed during heterotopic noxious stimulation of the symptomatic side of the body whereas stimulation of the sensate side elicited a DNIC response [13]. Such findings bear a striking resemblance to those of the CRPS patients in the present study. Since parts of the medulla play a major role in DNIC, deficits in inhibitory control from this region may account for the present findings. Nonetheless, the disparate pattern of sensory disturbances in the two conditions (hemilateral tactile deficits in CRPS compared with ipsilateral tactile forehead deficits in concert with below-neck contralateral tactile deficits in Wallenberg syndrome) seems inconsistent with this.

DNIC is triggered by the activation of Aδ- and C-fibers [4]. The ascending part of the DNIC loop occurs predominantly in the ventrolateral quadrant contralateral to the noxious stimulus [56]. Lesioning this quadrant of the cervical cord in rats produces a pattern of DNIC deficit similar to that in the present study [56]. In animals with left-sided lesions, the remote inhibitory DNIC effect from stimulation of the right hindpaw was strongly reduced whereas the lesion did not affect activation of DNIC from stimulation of the left hindpaw [56]. Lesions of the dorsal, dorsolateral and ventromedial parts of the cervical cord did not produce such effects [56]. Thus, the present findings suggest that DNIC-related transmission in the afferent pathway from the symptomatic limb (e.g., in the ipsilateral dorsal horn or contralateral ventrolateral quadrant) may be disrupted in CRPS.
Both the spinothalamic tract (that relays nociceptive information to the cerebral cortex) and the spinoreticular tract involved in DNIC contain projections from lamina V wide dynamic range neurons [8]. Perhaps failure to inhibit activity in the wide dynamic range neurons that receive input from the CRPS-affected limb ultimately sensitizes thalamic or cortical neurons that receive convergent information from hemilateral body sites. This could account for heightened sensitivity to stimulation of not only the affected limb but also other hemilateral regions.

The present findings also support the view that even more widespread disruptions of inhibitory pain control are involved in the pathogenesis of CRPS [47]. The inhibitory effects on forehead sensations during stimulation of the healthy limb were delayed and weak compared to those observed in healthy volunteers during a similar 2°C cold pressor [25]. In healthy volunteers, analgesia to pressure-pain sensations developed bilaterally in the forehead immediately after cold water immersion of the hand, whereas analgesia was absent until 10 minutes after the cold pressor in the CRPS patients in the present study. An immediate analgesic effect during the cold pressor was observed for pain in the symptomatic limb in the present study, but the reduction in pain subsided immediately upon removal of the healthy limb from the cold water. Together, these findings suggest that inhibitory pain control is compromised to stimulation of the unaffected side of the body in CRPS. The source of this deficit is uncertain but could involve cells in the subnucleus reticularis dorsalis that respond to stimulation at any body site, as DNIC was diminished both on the symptomatic and non-symptomatic sides of the body. It is interesting to note that noxious stimuli also evoke diffuse noxious excitatory controls from the dorsal reticular nucleus in the caudal medulla [1]. Thus a dysfunction in inhibitory control in CRPS may unmask pain facilitation. A shift toward facilitation in other diffuse bidirectional pain
control mechanisms such as serotonergic projections from raphe nuclei [61] may also play a role in CRPS, in particular during immersion of the affected limb as immersion of this limb failed to inhibit pain elsewhere in the body.

During cold water immersion in healthy volunteers, a stronger analgesia to pressure-pain was observed in the forehead ipsilateral to the immersed hand than in the contralateral forehead [25]. This analgesic component was lacking in the present study. We speculated that coeruleospinal pain modulation normally acts in concert with DNIC and perhaps stress-induced analgesia to produce ipsilateral forehead analgesia in healthy volunteers. In coeruleospinal pain control, noradrenergic projections from the locus coeruleus (LC) produce central inhibition via actions at $\alpha_2$-adrenoceptors [22; 23]. In a rat model of unilateral carageenan-induced hindpaw inflammation, activity emanating from the LC was observed proximally as well as distally in the ipsilateral dorsal horn, but not the contralateral dorsal horn [50-54]. Tsuruoka et al. [54] measured the thermal response threshold on all four paws of the rat during unilateral hindpaw inflammation and found shorter paw withdrawal latencies for both the inflamed hindpaw and the non-inflamed, but hyperalgesic, ipsilateral forepaw in rats with bilateral LC lesions than in sham-operated rats. Responses to contralateral stimulation remained unchanged. Curiously, CRPS patients display hyperalgesia of the ipsilateral forehead, in particular to pressure-pain [16], consistent with hemilaterally extending pain facilitation. Pressure hyperalgesia of the ipsilateral forehead was also present in the current sample of CRPS patients. The presence of hemilaterally descending facilitation in CRPS would be consistent with the findings by Seifert and colleagues [46] of heightened pain facilitation in the affected but not the unaffected limb.
Differential analgesic effects to cold water immersion were observed for pressure-pain and sharpness sensations. Dissociations between such sensations have been documented in healthy volunteers [25] and in clinical populations such as CRPS patients [16], central post-stroke pain patients [32] and patients with thalamic lesions [41]. Separate central representations may thus account for cutaneous versus deep tissue sensitivity. Consistent with this, cutaneous nociceptors appear to project predominantly to laminas I and II of the dorsal horn [59] whereas deep tissue nociceptors innervate laminas I and V [10; 33; 38]. In addition, different brain regions appear to be activated during superficial versus deep pain [21].

A limitation of this study is that patients remained on their usual pain medication. However, if anything, medication should have promoted analgesia during immersion of the CRPS-affected limb. A second limitation is that most patients were studied a year or more after CRPS onset, possibly when CRPS was maintained by secondary changes. It would be interesting to compare pain modulation processes in the early and advanced stages of CRPS.

In conclusion, central inhibitory pain control appears to be disrupted in CRPS to noxious stimulation on the CRPS-affected side of the body whereas inhibitory pain control to stimulation on the healthy side seems to be intact, although somewhat impaired. This disruption could unmask pain facilitation and thus promote central sensitization in nociceptive pathways. Brain imaging studies have shown that cortical centres involved in nociceptive processing are hyperactive during painful stimulation of the affected limb [24; 30; 31], consistent with central sensitization. In addition, the area in the somatosensory cortex representing the affected upper limb shrinks and shifts towards the adjacent cortical region representing the lip [24], particularly in patients with intense pain and mechanical
hyperalgesia [30]. This cortical reorganization appears to disrupt normal sensory processing [40]. Uncontrolled sensitization of spinal and supraspinal neurons which receive convergent input from hemilateral body sites may contribute to the ipsilateral spread of hyperalgesia in CRPS.


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### Symptom History as Reported by Patients

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Symptom history as reported by patients. Signs of disturbances noted during the initial physical examination are italicized in bold. A blank space indicates a lack of that particular symptom. **Limb** LU, left upper extremity; RU, right upper extremity; LL, left lower extremity; RL, right lower extremity. **Sensory disturbances** reported by patients included hyperalgesia, allodynia and numbness. Numbness was reported by all but six patients (Nos. 4, 10, 23, 24, 30, 32). The extent of hyperalgesia (to punctate stimulation) and allodynia (to brushing) in the symptomatic and the contralateral healthy limb was determined during an initial physical examination. Sharpness was rated in response to a single application of a firm nylon bristle (Filament 17, Senselab von Frey Aesthesiometer, Somedic Sales AB, Sweden) on a scale from 0 (not sharp) to 10 (stabbing). The bristle was applied with sufficient force to bend it for 1 s. Punctate hyperalgesia was defined as a sharpness rating at least 2 higher on a 0-10 scale in the affected than

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the unaffected limb. Patients rated the sensation to 3-4 light backwards-forwards strokes with a small brush as a normal or abnormal sensation. A qualitative description of the sensation was given by patients, when the brush felt abnormal. Descriptions of the brushing as uncomfortable, scratching or painful were regarded as allodynia. Two patients reported a numb sensation to the brushing (Nos. 24, 36). *Vasomotor and sudomotor disturbances* reported by patients were asymmetrical temperature sensations, dyschromia and hyperhidrosis. Limb temperature was also obtained from both the symptomatic and the equivalent healthy limb. This was done after the patient had rested quietly for at least 20 minutes in a room maintained at 20 ± 2°C. The temperature of the first phalanx of each toe was determined in lower limb CRPS patients, whilst the equivalent was obtained in the fingers of patients with upper limb pain, using an infrared skin thermometer (Tempett IR Thermometer, Somedic Sales AB, Sweden). A temperature difference greater than 1°C was regarded as asymmetrical (e.g., a hot or cold limb) and is *italicized in bold*. Swelling was reported by all patients except one (No. 28). *A decreased range of movement* was observed and reported by all but three patients (Nos. 7, 23, 28). Other *motor disturbances* reported by patients included weakness (all but patient no. 36), tremor and dystonia. *Trophic changes* (hair, nails, skin) varied greatly between patients.
Fig. 1. Pain and distress ratings in the healthy limb during healthy limb immersion and in the symptomatic limb during symptomatic limb immersion. A similar degree of pain and distress was experienced during immersion of the two limbs although both pain and distress decreased at a faster rate upon cold water removal of the healthy limb than the symptomatic limb resulting in greater pain and distress to immersion of the symptomatic limb after the CP and 2 min after the CP respectively. Error bars indicate standard errors and the arrow represents the CP.
Fig. 2. PPTs and sharpness ratings in the forehead ipsilateral and contralateral to the CRPS-affected limb before and for 12 min after cold water immersion of the healthy limb versus the symptomatic limb. During CP of the healthy limb, forehead sensitivity to pressure-pain initially increased (# p < 0.1 compared to baseline) but subsequently decreased (# p < 0.1 compared to baseline). In contrast, forehead sensitivity to pressure-pain increased and persisted immediately after immersion of the symptomatic limb (* p < 0.05 compared to baseline). No changes were observed for sharpness sensations. Error bars indicate standard errors and the arrow represents the CP.
Fig. 3. Clinical pain ratings in the symptomatic limb in response to cold water immersion of the contralateral healthy limb. Pain decreased significantly during immersion of the healthy limb (* p < 0.05), but returned to pre-immersion levels upon removal of the healthy limb from the water. Error bars indicate standard errors and the arrow represents the CP.
A. Healthy Limb Immersion

B. Symptomatic Limb Immersion

C. Healthy Limb Immersion

D. Symptomatic Limb Immersion
Fig. 4. PPTs and sharpness ratings in the healthy limb and the CRPS-affected limb before and for 12 min after cold water immersion of the healthy limb versus cold water immersion of the symptomatic limb. PPTs and sharpness ratings were not influenced during immersion of either limb. Error bars indicate standard errors and the arrow represents the CP.
CHAPTER 11

HEMILATERAL PRESSURE HYPERALGESIA: A SPECIFIC SIGN IN COMPLEX REGIONAL PAIN SYNDROME?

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Pages: 28
Tables: 2
Figures: 3

Key words: complex regional pain syndrome; pain laterality; neuropathic pain; nociceptive pain; back pain
Abstract

Sensory disturbances commonly spread outside the affected limb to the ipsilateral forehead in patients with complex regional pain syndrome (CRPS). To investigate whether this is a unique characteristic of CRPS or whether it occurs in other pain conditions, pressure-pain thresholds and sharpness sensations to a firm bristle were assessed on each side of the forehead, at the pain site and at an equivalent site on the contralateral side of the body in 35 chronic pain patients without CRPS (with neuropathic or nociceptive limb pain, back pain, or acute herpes zoster/postherpetic neuralgia). Findings were compared with similar assessments in 34 patients with CRPS. Ipsilateral forehead hyperalgesia to pressure-pain was present in a greater proportion of CRPS (59%) than non-CRPS patients (14%). Thirty-eight percent of CRPS patients also reported ipsilateral forehead hyperalgesia to sharpness. Ipsilateral forehead hyperalgesia both to sharpness and pressure-pain was, nonetheless, present in a minority of non-CRPS patients. In general, heightened sensitivity to pressure and sharpness in the ipsilateral forehead was present in patients with greater pain, sharpness hyperalgesia and swelling at the pain site. Inflammation-induced sensitization of spinal and supraspinal neurons, perhaps heightened by abnormal central pain control, could underlie the hyperexcitability to stimulation both at the pain site and in the ipsilateral forehead. Ipsilateral forehead hyperalgesia to pressure-pain was more prevalent in patients with a longer duration of CRPS, suggesting that mechanisms that predominate in the later stages of the disease mediate the spread of hyperalgesia from the affected limb to more distant sites.
Introduction

Complex regional pain syndrome (CRPS) is a condition characterised by regional pain and sensory disturbances (hyperalgesia, allodynia and sensory loss) as well as disturbances in autonomic and motor systems [2; 16; 44]. Theories about the pathology underlying CRPS include exaggerated neurogenic inflammation, sympathetic nervous system dysfunction (adrenergic supersensitivity, sprouting of adrenergic receptors) and central sensitization and disinhibition.

In CRPS, sensory disturbances commonly spread outside the affected limb [11; 35; 36; 40]. A hemilateral or quadratomal loss of sensitivity to tactile stimulation (pinprick, touch, thermal thresholds) was documented in 50% of CRPS patients [35; 36; 40] and hyperalgesia to pressure-pain was documented in the ipsilateral forehead in 78% of patients [11]. Sensations of sharpness to pinprick in the ipsilateral forehead were associated with similar sensations in the affected limb [11]. Hemilateral sensory disturbances were suggested to be characteristic of CRPS with a potential for diagnostic use [11].

Sensory disturbances may also spread in chronic pain conditions other than CRPS [28]. Levy and Munchin [25] and Moldofsky and England [30] reported on small samples of ‘hysterical anesthesia’ patients (nine and five patients respectively) with hemianesthesia or hemihypoesthesia. Fishbain et al. [14] documented non-dermatomal sensory loss in 40.4% of 247 patients with myofascial pain syndrome, but did not report the location of the abnormalities or the type of assessments conducted. In a study of 194 patients, most with fibromyalgia, 49 patients (25.3%) presented with deficits to pinprick in a hemilateral or quadratomal pattern on the side of pain or worst pain [29]. Pressure-pain thresholds were either elevated or reduced. Fibromyalgia, by definition, is a generalized pain condition which might explain the widely distributed sensory disturbances to pressure and pinprick.
Similar arguments can be made for myofascial pain syndrome. Rommel et al. [37] have since described two radiculopathy patients with sensory loss to touch, pain and temperature on the entire ipsilateral side of the body; however, the case report nature of this study limits its generalisability.

To determine the specificity of hemilateral sensory disturbances to CRPS, it is important to establish whether sensory disturbances occur outside the area of pain in a larger group of patients with more localized chronic pain than fibromyalgia or myofascial pain syndrome. The aim of this study was to investigate sensory disturbances to pressure and pinprick on each side of the forehead in patients with chronic non-CRPS pain limited to one side of the body, and to compare the findings with those of CRPS patients. In addition to shedding light on the diagnostic utility of hemilateral sensory disturbances for CRPS, such investigations may also help shed light on mechanisms underlying the spread of sensory disturbances.

Method

Participants

Thirty-five chronic pain patients without CRPS participated in the study. They were recruited from local hospitals and pain clinics based on prior medical diagnoses. Unilateral pain was a pre-requisite in all patients. Three patients had acute herpes zoster (HZ) and 8 had postherpetic neuralgia (PHN), 6 patients suffered from neuropathic limb pain and 11 patients from nociceptive limb pain (8 osteoarthritis, 2 tendinosis, 1 blood clot). Another 7 patients experienced lower back pain from disc protrusion/degeneration which radiated down to the toes (3 patients), knee (1 patient) or occasionally the thigh (2 patients) of one limb. These patients were compared to 34 patients with unilateral CRPS seen by the
investigators over the past three years (CRPS I: 32 patients, CRPS II: 2 patients).
Symptoms were assessed according to the CRPS criteria (Table 1) [17] to establish whether such symptoms were associated with unilaterally extending sensory disturbances. Patients were not required to abstain from routine medication during the trial due to the practical and ethical concerns relating to this. Medication use amongst CRPS and non-CRPS patients included analgesics, anticonvulsants and/or antidepressants. The proportion of patients on medication did not differ between CRPS patients and the other pain patients (Table 1), although fewer back pain patients received medication for their pain. The Murdoch University Human Research Ethics Committee approved the study and written informed consent was obtained from each participant.

Procedure

Tests of sensation. Pressure-pain thresholds (PPTs) and sharpness sensations to stimulation with a firm bristle were assessed on each side of the forehead, as well as at the site of pain [13]. In back pain patients, this was always the lumbar region. In HZ/PHN patients the upper back or chest was usually the site of testing. The dorsal hand or foot was assessed in limb pain patients. An equivalent location on the contralateral side of the body was also assessed. Pressure was applied using a spring loaded algometer with a rounded tip (1 cm in diameter). Pressure was applied in 80 g increments to the forehead and 200 g increments elsewhere until participants reported the onset of pain or to a maximum of 2.3 kg [13]. Only 9 patients tolerated the maximum pressure, usually in the unaffected limb (8 patients). Sharpness was rated on a scale from 0 (not sharp) to 10 (stabbing) in response to a single application with a firm nylon bristle (Filament 17, Senselab von Frey Aesthesiometer, Somedic Sales AB, Sweden) [13]. The bristle was applied until it bent for 1 s. The bristle was tolerated by all patients.
Statistical approach

Differences in sensitivity to pressure-pain and sharpness between the ipsilateral and contralateral forehead of patients without CRPS were investigated in Forehead side (ipsilateral forehead versus contralateral forehead) x Pain location (limb pain versus torso pain) x Pain type (nociceptive pain versus neuropathic pain) analyses of variance. As findings from these analyses were similar irrespective of pain location or type of pain, the non-CRPS patients were grouped together in subsequent analyses. Thus, Forehead side (ipsilateral forehead versus contralateral forehead) x Pain group (non-CRPS versus CRPS) analyses of variance compared non-CRPS patients to CRPS patients on sensitivity to pressure-pain and sharpness in the ipsilateral versus the contralateral forehead. Analysis of variance generally is robust to violations of normality. However, as some data did not fit a normal bell-shaped curve, the non-parametric Wilcoxon’s signed-ranks sum test was employed to investigate significant interactions.

Sensitivity to pressure-pain and sharpness normally differs slightly between the right and left side of the forehead in healthy individuals [22]. To determine the proportion of patients with ipsilateral forehead hyperalgesia or ipsilateral forehead analgesia amongst CRPS and non-CRPS patients, the absolute difference in sensitivity between the right and left side of the forehead in a sample of 141 healthy volunteers (96 females (68%), mean age = 24.00 ± 0.61 years), examined by the authors previously, provided a comparison. As the healthy sample data for pressure-pain was positively skewed, a difference outside that of the 80th percentile of the healthy volunteers (160 g or above) was considered unusual (i.e., ipsilateral forehead hyperalgesia or ipsilateral forehead analgesia). As the absolute difference in forehead sensitivity to sharpness was more homogenous, the 90th percentile provided the cut-off point for sharpness (a difference of 2 points on the VAS or above). Pearson’s chi-square, or in the case of small expected frequency counts, Fisher’s exact test,
was used to explore differences in the proportion of patients with ipsilateral forehead hyperalgesia to pressure-pain, and sharpness, in the CRPS versus the non-CRPS group. Similar analyses were performed for ipsilateral forehead analgesia and symmetrical (within normal range) forehead sensitivity.

To determine the factors (gender, age, pain intensity, pain duration, hyperalgesia to sharpness and pressure at the pain site, swelling, hyperhidrosis, dyschromia, motor disturbances (absent, mild, severe) and trophic disturbances (absent, present)) that distinguished people with ipsilateral forehead hyperalgesia from patients without, Mann-Whitney U tests or Fisher’s exact tests, as appropriate, were employed. The presence of dystonia denoted severe motor disturbances while the presence of tremor and/or limited range of movement denoted mild motor disturbances. These analyses were performed separately for the CRPS patients and non-CRPS patients to determine whether similar factors were associated with ipsilateral forehead hyperalgesia in both groups. Back pain patients and HZ/PHN patients were excluded from the analyses of hyperalgesia at the pain site due to the potential confound of differences in sensitivity at the testing site (limbs vs. torso). Data is presented as the mean ± standard error of the mean.

Results

Irrespective of pain location (limb versus torso), and whether the pain was nociceptive or neuropathic in origin, no difference in sensitivity to pressure-pain was observed between the ipsilateral and contralateral forehead in the non-CRPS patients. However, greater sharpness ratings to pinprick in the ipsilateral forehead was observed (Fig. 1) [main effect for Forehead Side F(1,31) = 4.62, p = 0.039].
In contrast, sensitivity to pressure-pain was greater in the ipsilateral than the contralateral forehead of patients with CRPS consistent with ipsilateral forehead hyperalgesia (Fig. 1A) [Wilcoxon’s $Z = -3.12$, $p = 0.002$] [Forehead Side x Pain group interaction $F(1, 67) = 11.43$, $p = 0.005$]. Like the non-CRPS patients, CRPS patients reported greater sharpness ratings to punctate stimulation in the ipsilateral forehead (Fig. 1B) [main effect for Forehead Side $F(1,67) = 9.80$, $p = 0.003$].

The proportion of patients with ipsilateral forehead hyperalgesia or analgesia to pressure-pain is shown in Figure 2. The majority of CRPS patients displayed ipsilateral forehead hyperalgesia to pressure-pain (59%) (Fig. 2A). This was a significantly greater proportion than in the non-CRPS group (14%) [X$^2 = 14.81$, $p = 0.000$]. Conversely, forehead sensitivity to pressure was symmetrical in the majority of non-CRPS patients (69%) (Fig. 2B). This was a greater proportion than in the CRPS group (26%) [X$^2 = 12.25$, $p = 0.000$]. The proportion of patients with ipsilateral forehead analgesia to pressure in the non-CRPS group (17%) was similar to that in the CRPS group (15%) (Fig. 2C).

As shown in Figure 3, the CRPS patients did not differ greatly from the non-CRPS group in the proportion of patients with asymmetrical forehead sensations to sharpness. Ipsilateral forehead hyperalgesia to sharpness was present in 38% of CRPS patients and 26% of non-CRPS patients (Fig. 3A), but symmetrical forehead sensitivity to sharpness generally seemed to dominate amongst both CRPS (50%) and non-CRPS patients (66%) (Fig. 3B).

Both CRPS and non-CRPS patients with ipsilateral forehead hyperalgesia generally reported heightened sensitivity at the pain site (Table 2). CRPS patients with ipsilateral forehead hyperalgesia to pressure or sharpness reported, respectively, greater sharpness hyperalgesia in the affected limb and greater pain in the affected limb than the remaining CRPS patients. In addition, non-CRPS patients with sharpness hyperalgesia in the
ipsilateral forehead reported greater hyperalgesia to sharpness at the pain site than non-CRPS patients without ipsilateral forehead hyperalgesia. Non-CRPS patients with ipsilateral forehead hyperalgesia to pressure were also more likely to describe swelling at the pain site (Table 2). All CRPS patients with ipsilateral forehead hyperalgesia to pressure similarly reported swelling in their affected limb, but so did 93% of the remaining CRPS patients. Finally, CRPS patients with ipsilateral forehead hyperalgesia to pressure reported a longer duration of pain and, probably for similar reasons, were older than CRPS patients without ipsilateral forehead hyperalgesia to pressure (Table 2).

Discussion

This study confirmed previous findings of ipsilateral forehead hyperalgesia in CRPS [11; 13]. Ipsilateral forehead hyperalgesia to pressure-pain was present in the majority of CRPS patients (59%) and sharpness hyperalgesia was present in the ipsilateral forehead in 38% of patients with CRPS. In contrast, forehead sensitivity to pressure-pain and sharpness was symmetrical in most non-CRPS patients (69%). Ipsilateral forehead hyperalgesia both to sharpness (26%) and pressure-pain (14%) was, however, detected in a few of these patients. These findings suggest that the utility of ipsilateral forehead hyperalgesia to pressure-pain in the diagnosis of CRPS warrants further investigation.

The mechanism underlying the ipsilateral forehead hyperalgesia is unclear, but a similar mechanism probably mediates heightened sensitivity at the pain site. Sharpness hyperalgesia at the pain site was greater both in CRPS patients with ipsilateral forehead hyperalgesia to pressure-pain and in non-CRPS patients with ipsilateral forehead hyperalgesia to sharpness than in other patients. In addition, CRPS patients with ipsilateral forehead hyperalgesia to sharpness reported greater pain in the affected limb. Ipsilateral
forehead hyperalgesia to pressure-pain or sharpness was also previously associated with heightened sensitivity in the affected limb to stimuli such as pinprick or thermal hot or cold [11; 13].

Possible mechanisms underlying the spread of hyperalgesia from the affected limb to the forehead in CRPS may include sensitization of spinal or supraspinal nociceptive neurons or disruption of central pain modulating processes. Cortical nociceptive input from the affected limb (e.g., during mechanical hyperalgesia) is heightened [21; 26; 27; 43] and cortical representation of the symptomatic limb is reduced [21; 26; 33]. Mean sustained pain levels over several weeks were associated with the extent of cortical reorganisation [33], consistent with sensitization of spinal or supraspinal neurons to nociceptive input from the CRPS-affected limb. Central pain modulating mechanisms also appear to be compromised in CRPS [9; 10; 39]. A dysfunction in inhibitory pain control could promote the transfer of nociceptive messages to higher brain centres. Increased excitability at brain sites that receive convergent input from hemilateral body sites such as the contralateral thalamus or somatosensory cortex could underlie the heightened sensitivity to stimulation both in the affected limb and the ipsilateral forehead. In addition, a shift toward facilitation for mechanisms with a bidirectional role in pain control, such as the noradrenergic actions from the locus coeruleus, the serotonergic actions from the raphe nuclei or diffuse noxious facilitatory versus inhibitory controls, may increase the excitability of both spinal and supraspinal neurons [1; 18; 20; 47; 48]. In particular, noradrenergic projections from the locus coeruleus, which were detected only in the ipsilateral and not in the contralateral dorsal horn during unilateral carageenan-induced hindpaw inflammation in the rat [41], could contribute to central facilitation hemilaterally via actions at $\alpha_1$-adrenoceptors in the dorsal horn [18].
The majority of non-CRPS patients with ipsilateral forehead hyperalgesia to pressure-pain described swelling at the pain site. As all CRPS patients with ipsilateral pressure hyperalgesia in the forehead also described swelling, it is tempting to speculate that inflammation at the pain site, perhaps in conjunction with hyperalgesia, contributes to the spread of sensory disturbances. Exaggerated neurogenic inflammation is postulated to play a crucial role in the generation of CRPS [3; 4; 23; 45]. Many CRPS symptoms such as swelling, hyperhidrosis, dyschromia and trophic changes are consistent with inflammation. These symptoms were generally present in a greater proportion of CRPS patients than non-CRPS patients in the present study, and could thus be linked with the increased prevalence of sensory disturbances in the forehead in the CRPS group. During inflammation, the activation threshold of dorsal horn neurons decreases and their receptive fields and responsiveness increase in response to continuous C fiber input to the superficial layers of the dorsal horn [6]. This could provide a mechanism by which inflammation facilitates the excitability of spinal and/or supraspinal neurons. Consistent with this, carageenan-induced hindpaw inflammation in the rat decreased paw withdrawal latencies to thermal stimuli both in the inflamed hindpaw and the non-inflamed ipsilateral forepaw [42]. However, inflammation alone cannot explain the ipsilateral spread of hyperalgesia in CRPS because the affected limb was swollen in most CRPS patients, including those without ipsilateral forehead hyperalgesia. Ipsilateral forehead hyperalgesia to pressure-pain was associated with a greater duration of CRPS, suggesting that mechanisms that predominate in the later stages of the disease mediate the spread of hyperalgesia from the affected limb to more distant sites.

Ipsilateral forehead hyperalgesia to pressure-pain or sharpness was detected in a minority of non-CRPS patients. Sensitization of spinal nociceptive neurons and
reorganisation in the somatosensory cortex might also contribute to the spread of sensations in these patients [8; 12; 15; 32; 38] as may central disinhibition [5; 19; 24; 31; 46], perhaps maintained by inflammation (swelling) at the pain site.

A hemilateral sensory loss, mainly to tactile stimuli, was reported previously in CRPS, fibromyalgia and myofascial syndrome patients [14; 29; 35]. Analgesia to pressure-pain or sharpness was present in the ipsilateral forehead in a small number of CRPS (pressure: 15%; sharpness: 12%) and non-CRPS patients (pressure: 17%; sharpness: 8%) in the present study. The small proportion of patients with these sensory disturbances did not permit analysis of the factors contributing to this type of spread. However, brain imaging studies have shown that in CRPS patients with intense pain and hyperalgesia, the area in the somatosensory cortex representing the affected upper limb shrinks and shifts towards the adjacent cortical region representing the lip [21; 26]. Thus, cortical reorganization could disrupt normal sensory processing [34]. The involvement of cortical reorganisation in fibromyalgia and myofascial pain syndrome remains to be investigated.

The present study assessed a similar number of CRPS and non-CRPS patients. The sampling of non-CRPS patients with a variety of pain types (e.g., neuropathic pain, nociceptive pain, back pain, HZ/PHN) is both a strength and a limitation of the study. Assessing forehead sensitivity across a variety of conditions provides an indication of the prevalence of hemilateral sensory disturbances in the general non-CRPS pain population, but the small number of participants within each diagnostic category limits the generalisability of the results for each of these diagnostic groups. Thus, further studies of ipsilateral forehead sensory disturbances in larger samples of each pain condition are encouraged. These studies should aim to employ objective measures of sign severity to investigate whether ipsilateral forehead sensory disturbances (i.e., hemilateral hyperalgesia)
are better determined by such objective measures than the subjective symptom reports provided by patients in the present study.

Due to the demographic features of CRPS [7], more females were present in the CRPS group than the non-CRPS group, and they generally were younger. The prevalence of CRPS in females is widely recognised and is unlikely to have contributed to the results as the proportion of males and females was similar in patients with and without ipsilateral forehead hyperalgesia. Age is also unlikely to underlie the greater occurrence of ipsilateral forehead hyperalgesia in CRPS patients as patients with ipsilateral forehead hyperalgesia were generally older, not younger. Finally, although medication use may have affected the results, medication use was similar in the CRPS and non-CRPS conditions and is thus unlikely to account for the increased prevalence of sensory disturbances in the ipsilateral forehead of CRPS patients.

In conclusion, the majority of CRPS patients reported ipsilateral forehead hyperalgesia to pressure-pain whereas differences in sensitivity to pressure-pain in the ipsilateral and contralateral forehead were within the normal range in the majority of non-CRPS patients. Sensitization of spinal and/or supraspinal neurons that receive convergent input from hemilateral body sites could explain hyperexcitability both to stimulation in the affected limb and the ipsilateral forehead, and could arise from a failure of pain control mechanisms to control the sensitization of central nociceptive neurons during inflammation. A shift toward facilitation in pain control mechanisms could further contribute to increased excitability of central nociceptive neurons.
References


Table 1
Sensory, vasomotor/sudomotor and motor/trophic disturbances reported by CRPS patients and patients with neuropathic limb pain, HZ/PHN, nociceptive limb pain and back pain

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Pain Groups</th>
<th>CRPS (N = 34)</th>
<th>Limb (N = 6)</th>
<th>HZ/PHN (N = 11)</th>
<th>Limb (N = 11)</th>
<th>Back (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>82%</td>
<td>0%***</td>
<td>36%**</td>
<td>46%*</td>
<td>29%***</td>
</tr>
<tr>
<td><strong>Age (years)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>40.38 ± 2.11</td>
<td>51.33 ± 3.57***</td>
<td>70.00 ± 3.39***</td>
<td>45.91 ± 4.55</td>
<td>58.57 ± 6.68*</td>
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<tr>
<td><strong>Pain intensity (0-10)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.13 ± 0.37</td>
<td>5.50 ± 0.41</td>
<td>3.86 ± 0.72</td>
<td>4.27 ± 0.78</td>
<td>4.36 ± 0.94</td>
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<tr>
<td><strong>Pain duration (months)</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24.50</td>
<td>49.50</td>
<td>3.00</td>
<td>32.00</td>
<td>24.00</td>
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<tr>
<td></td>
<td>(range 2-186)</td>
<td>(range 17-420)</td>
<td>(range 0.50-132)**</td>
<td>(range 3-216)</td>
<td>(range 6-90)</td>
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<tr>
<td><strong>Sensory changes</strong></td>
<td></td>
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<tr>
<td>Hypoesthesia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79%</td>
<td>83%</td>
<td>36%*</td>
<td>46%*</td>
<td>29%*</td>
<td></td>
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<tr>
<td>Hyperalgesia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>97%</td>
<td>67%*</td>
<td>64%**</td>
<td>73%*</td>
<td>29%***</td>
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<tr>
<td>Allodynia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>97%</td>
<td>67%*</td>
<td>82%</td>
<td>36%***</td>
<td>0%***</td>
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<tr>
<td><strong>Vasomotor/sudomotor</strong></td>
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<tr>
<td>Swelling&lt;sup&gt;a&lt;/sup&gt;</td>
<td>97%</td>
<td>33%***</td>
<td>27%***</td>
<td>55%**</td>
<td>29%***</td>
<td></td>
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<tr>
<td><strong>Temperature sensation</strong></td>
<td></td>
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<tr>
<td>Cold&lt;sup&gt;a&lt;/sup&gt;</td>
<td>56%</td>
<td>0%*</td>
<td>0%***</td>
<td>18%*</td>
<td>0%**</td>
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<td>Hot&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18%</td>
<td>33%</td>
<td>36%</td>
<td>27%</td>
<td>14%</td>
<td></td>
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<tr>
<td>Interchanging temperature&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td><strong>Dyschromia</strong></td>
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<tr>
<td>Flushed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15%</td>
<td>17%</td>
<td>36%</td>
<td>27%</td>
<td>0%</td>
<td></td>
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<tr>
<td>Cyanotic&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15%</td>
<td>17%</td>
<td>9%</td>
<td>18%</td>
<td>0%</td>
<td></td>
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<tr>
<td>Interchanging dyschromia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>53%</td>
<td>0%*</td>
<td>9%**</td>
<td>0%***</td>
<td>0%**</td>
<td></td>
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<tr>
<td>Hyperhidrosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79%</td>
<td>17%**</td>
<td>0%***</td>
<td>18%***</td>
<td>0%***</td>
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<tr>
<td>Hypohidrosis</td>
<td>0%</td>
<td>0%</td>
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<td>0%</td>
<td>0%</td>
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<td><strong>Motor/trophic</strong></td>
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<td></td>
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<tr>
<td>Limited range of movement&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91%</td>
<td>67%</td>
<td>9%***</td>
<td>64%*</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Weakness&lt;sup&gt;a&lt;/sup&gt;</td>
<td>97%</td>
<td>67%*</td>
<td>9%***</td>
<td>91%</td>
<td>57%**</td>
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<tr>
<td>Tremor&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79%</td>
<td>33%*</td>
<td>18%***</td>
<td>46%*</td>
<td>0%***</td>
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<tr>
<td>Dystonia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12%</td>
<td>0%</td>
<td>0%</td>
<td>9%</td>
<td>0%</td>
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<tr>
<td><strong>Hair growth</strong></td>
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<tr>
<td>Less&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18%</td>
<td>17%</td>
<td>0%</td>
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<td>0%</td>
<td></td>
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<tr>
<td>More&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12%</td>
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<td>0%</td>
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<tr>
<td><strong>Nail growth</strong></td>
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</table>
Symptom percentages indicate the percentage of patients in the pain group who reported the presence of the respective symptom. \(^a\)Fisher’s exact test. \(^b\)Wilcoxon test. Significantly different from the CRPS group. \(^\# \)p < 0.07; \(* \)p < 0.05; \(** \)p < 0.01; \(*** \)p < 0.001.
Table 2
Factors distinguishing patients with ipsilateral forehead hyperalgesia to pressure-pain or sharpness from patients without ipsilateral forehead hyperalgesia, in the CRPS and non-CRPS conditions

<table>
<thead>
<tr>
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<th>Ipsilateral forehead hyperalgesia to pressure-pain</th>
<th>Ipsilateral forehead hyperalgesia to sharpness</th>
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<tr>
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<td>CRPS (Present N = 20) Absent (N = 14)</td>
<td>Non-CRPS (Present N = 5) Absent (N = 30)</td>
</tr>
<tr>
<td>Females</td>
<td>85% 79%</td>
<td>40% 30%</td>
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<tr>
<td>Age (years)</td>
<td>44.25 ± 1.88* 34.86 ± 4.00</td>
<td>64.20 ± 6.34 55.73 ± 3.05</td>
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<tr>
<td>Pain intensity</td>
<td>5.33 ± 0.52 4.86 ± 0.51</td>
<td>5.60 ± 0.81 4.17 ± 0.42</td>
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<tr>
<td>Pain duration</td>
<td>56.65 ± 10.65** 26.29 ± 9.46</td>
<td>29.60 ± 16.83 55.38 ± 15.37</td>
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<tr>
<td>Symptoms (pain site)</td>
<td></td>
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<tr>
<td>Pressure hyperalgesia (g)</td>
<td>-896 ± 143 -864 ± 160</td>
<td>-300 ± 100 -285 ± 168</td>
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<tr>
<td>Sharpness hyperalgesia (0-10)</td>
<td>3.73 ± 0.83 1.00 ± 1.15</td>
<td>3.06 ± 1.39 1.60 ± 0.78</td>
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<td>Swelling</td>
<td>100% 93%</td>
<td>80%* 30%</td>
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<td>Dyschromia</td>
<td>75% 93%</td>
<td>60% 33%</td>
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<td>Hyperhidrosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80%</td>
<td>79%</td>
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<tr>
<td>Motor (present (severe))&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90(10%)</td>
<td>86(14%)</td>
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<tr>
<td>Trophic&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90%</td>
<td>86%</td>
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<sup>a</sup>Fisher’s exact test, <sup>b</sup>Mann-Whitney U test. <sup>c</sup>Back pain patients and HZ/PHN patients excluded from analyses. Difference statistically significant. # p < 0.07; * p < 0.05; ** p < 0.01.
Fig. 1. Pressure-pain thresholds and sharpness ratings in the affected and unaffected pain site and in the ipsilateral and contralateral forehead in each pain group (CRPS, neuropathic limb pain, HZ/PHN, nociceptive limb pain and back pain).
Fig. 2. Proportion of CRPS, neuropathic limb pain, HZ/PHN, nociceptive limb pain and back pain patients with ipsilateral forehead hyperalgesia, symmetrical forehead sensations and ipsilateral forehead analgesia to pressure-pain.
A. Ipsilateral Forehead Hyperalgesia

B. Symmetrical Forehead Sensations

C. Ipsilateral Forehead Analgesia
Fig. 3. Proportion of CRPS, neuropathic limb pain, HZ/PHN, nociceptive limb pain and back pain patients with ipsilateral forehead hyperalgesia, symmetrical forehead sensations and ipsilateral forehead analgesia to sharpness.
CHAPTER 12

CONCLUSIONS

12.1 Summary of the seven studies

The aim of this thesis was to investigate potential mechanisms involved in the spread of sensory disturbances outside the affected limb in complex regional pain syndrome (CRPS). The experiments in chapter 5 investigated the effect of experimental limb pain (cold-induced limb pain) on sensory changes outside the limb on each side of the forehead in healthy volunteers. Prior to pain induction, differences in pressure-pain or sharpness sensitivity between the left and right side of the forehead were generally small or non-existent. The induction of limb pain in healthy volunteers produced a bilateral reduction in forehead sensations to pressure-pain and sharpness with greater analgesia to pressure in the ipsilateral forehead.

The second study attempted to disrupt inhibitory pain control prior to inducing limb pain (via cold noxious stimulation) in a sample of healthy volunteers, and investigated the effects of these procedures on sensitivity to pressure-pain and sharpness on each side of the forehead. The use of optokinetic stimulation to disrupt inhibitory control was based on previous findings of increased forehead sensitivity following this form of motion sickness-inducing stimulation [12; 13]. As in Study one, differences in forehead sensitivity to pressure-pain or sharpness between the left and right sides of the forehead were small or non-existent upon commencing the study. Despite a replication of increased forehead sensitivity to pressure-pain and sharpness during residual motion sickness, cold-induced limb pain reduced forehead sensitivity to these stimuli in the most pain sensitive participants, suggesting that inhibitory pain control mechanisms remained intact.
The third study performed in healthy volunteers explored the possibility of an association between limb inflammation and hemilateral hyperalgesia. Differences in sensitivity to pressure-pain or sharpness between the two sides of the forehead in this group of healthy volunteers were again generally small or non-existent, and the application of topical capsaicin, an inflammatory agent, to the forearm failed to produce an ipsilateral spread of hyperalgesia to the forehead. Instead, participants reported a reduction in sharpness ratings in the forehead bilaterally 6 hours after treatment, and a reduction in sensitivity to pressure-pain ipsilaterally when the treated area was heated after 48 hours of treatment.

Limitations of these three studies performed in healthy volunteers included the sample characteristics: mostly young, educated females. Nonetheless, gender and age did not appear to be a factor in the development of forehead analgesia. Besides, as CRPS is more prevalent in females [10], such characteristics are unlikely to account for any contrasting findings. Study three was also limited by a small sample size (17 participants). Nonetheless, the findings were consistent with those detected in the larger samples in Study one and two. Other limitations in these studies included reliance on self-report measures and that the experimenter was not blinded to the hypotheses. However, as patients were unaware of the specific hypotheses of the studies such influences were probably small. Finally, acute experimental pain in healthy volunteers may not be comparable to chronic pain.

CRPS patients were assessed in the remaining studies. In a double-blind placebo-controlled trial in Study four, the NMDA antagonist, topical ketamine, was applied to the affected or unaffected limb of patients with CRPS and the effect on sensitivity to a range of sensory stimuli (touch, pinprick, thermal, pressure, brushing) was investigated in the affected and unaffected limb and on each side of the forehead. Hyperalgesia to sharpness,
pressure, cold and heat, and allodynia to brushing, were detected in the ipsilateral forehead before treatment. This was generally associated with heightened sensitivity in the affected limb. The topical application of ketamine reduced allodynia and sharpness hyperalgesia in the affected limb. In some patients with allodynia in the forehead, forehead allodynia was also reduced following treatment of the affected limb with ketamine.

Study five investigated whether the increase in pain to acoustic startle is lateralized in CRPS patients. Acoustic startle in the ear ipsilateral to the affected limb induced greater pain than startle in the contralateral ear. In addition, auditory discomfort was greater to ipsilateral than contralateral ear stimulation and in patients with increased pain to startle than in a small group of non-responders.

Study six further explored the laterality of a dysfunction in inhibitory pain control in CRPS. Pressure-pain and sharpness sensations were investigated on each side of the forehead in CRPS patients during noxious cold stimulation of the affected limb versus noxious cold stimulation of the contralateral unaffected limb. Cold water immersion of the healthy limb produced bilateral forehead analgesia to pressure-pain and a reduction in clinical pain in the affected limb. However, pressure-pain increased in the forehead after immersion of the symptomatic limb. Sharpness ratings in the forehead remained unchanged to immersion of either limb.

Finally, pressure-pain and sharpness sensations were investigated on each side of the forehead in chronic pain patients without CRPS (neuropathic or nociceptive limb pain, back pain or acute herpes zoster/postherpetic neuralgia) and compared to similar measurements obtained in patients with CRPS. Ipsilateral forehead hyperalgesia to pressure-pain appeared to be more common in CRPS patients (59%) than patients without CRPS (14%) who generally reported symmetrical (within normal range) forehead sensations. Ipsilateral forehead hyperalgesia to sharpness occurred in 38% of CRPS patients.
which was similar to that in patients without CRPS. However, symmetrical sharpness sensations dominated in both groups. In general, heightened sensitivity to pressure and sharpness in the ipsilateral forehead was present in patients with greater pain, sharpness hyperalgesia and swelling at the pain site.

The main limitation of these studies included the recruitment of patients from pain specialists which may have resulted in a non-representative sample of severely-affected patients. In addition, some patients participated in more than one study which may have overemphasized the consistency of findings of ipsilateral forehead hyperalgesia in CRPS patients across studies (see Appendix A for details about which patients participated in which studies). Regular medication use was maintained by medicated patients in all studies and potentially could have affected the results. However, the main focus of this thesis was the hemilateral disturbances in the patients which are unlikely to have been influenced by the systemic effects of medication. Finally, limitations of self-report measures and lack of blinding of the experimenter also apply to the studies in CRPS patients. However, like the healthy volunteers, patients were unaware of the purpose of the studies rendering such influences unlikely. Both patients and the experimenter were blinded to the treatment with topical ketamine in Study four.

12.2 Implications for CRPS

Taken together the findings of this thesis suggest that:

1. ipsilateral forehead hyperalgesia, in particular to pressure-pain, may be specific to CRPS;

2. central sensitization evoked by nociceptive input from the inflamed CRPS limb may underlie the hyperalgesia at hemilateral body sites; and
3. Dysfunction in generalized and hemilateral pain control mechanisms, in particular to stimulation of the affected limb, may contribute to the hemilateral spread of sensory disturbances in CRPS.

1. Ipsilateral forehead hyperalgesia, in particular to pressure-pain, may be specific to CRPS.

   As demonstrated in Study one, two, and three, healthy volunteers generally report no or very little difference between the sides of the forehead in sensitivity to pressure-pain or sharpness. Symmetrical forehead sensitivity to pressure-pain and sharpness also dominated in chronic pain patients without CRPS (Study seven). In contrast, ipsilateral forehead hyperalgesia to pressure-pain was present in the majority of CRPS patients (Study seven). In a previous study, pressure-pain thresholds were similarly lower in the ipsilateral than contralateral forehead in 78% of patients with CRPS [14]. Although Study seven demonstrated ipsilateral forehead hyperalgesia to sharpness in only 38% of CRPS patients, Study four demonstrated greater sensitivity in the ipsilateral than the contralateral forehead of CRPS patients across a range of sensory modalities including sharpness (pressure-pain, cold pain, heat pain and allodynia to brushing). Thus, the further exploration of the utility of ipsilateral forehead hyperalgesia, in particular to pressure-pain, in the diagnosis of CRPS is warranted. Such diagnostic assessments are easily applied by health professionals in the clinical setting and could provide a viable diagnostic tool.

2. Central sensitization evoked by nociceptive input from the inflamed CRPS limb may underlie the hyperalgesia at hemilateral body sites.

   As described in chapter 3, exaggerated neurogenic inflammation to trauma or injury may be involved in the development of CRPS [4; 5; 25; 39; 40]. The sensitization of
peripheral nociceptors during inflammation results in increased nociceptive input to the dorsal horn which, in turn, promotes central sensitization [8]. Peripheral NMDA-receptors are involved in the sensitization of primary afferent nociceptors during inflammation [6; 15; 21] and could thus indirectly be involved in the sensitization of central neurons in CRPS. The topical application of the NMDA-antagonist, ketamine, to the CRPS-affected limb, in Study four, reduced allodynia and sharpness hyperalgesia in the affected limb. As allodynia to brushing the skin and sharpness hyperalgesia are mediated by sensitized spinal nociceptive and wide dynamic range neurons that receive input from nociceptive A-delta fibers and non-nociceptive A-beta fibers [26; 27], peripheral NMDA-receptors may play a role in the sensitization of central neurons in CRPS. The loss of alldynia in the ipsilateral forehead in some patients following the topical application of ketamine to the affected limb in Study four suggests that a similar mechanism may contribute to the heightened sensitivity in the forehead.

In CRPS, inflammatory processes may sensitize neurons in the dorsal horn and neurons at supraspinal sites that receive input from the affected limb such as the contralateral thalamus. Convergence of input from the affected limb and the ipsilateral forehead at this site could explain findings of an association between heightened sensitivity in the affected limb and heightened sensitivity in the ipsilateral forehead (Study four, five, and seven). Associations between heightened sensitivity in the affected limb and in the ipsilateral forehead were also demonstrated in a previous study [14].

In further support of a link between inflammatory processes and hemilateral hyperalgesia, swelling was present in all CRPS patients with ipsilateral forehead hyperalgesia to pressure-pain. Similarly, swelling was associated with ipsilateral forehead hyperalgesia to pressure in non-CRPS patients. Inflammation could thus play a role in the spread of hyperalgesia from the affected limb to the forehead in CRPS. Nonetheless, the
contribution of inflammation in the affected limb to the spread of hyperalgesia in CRPS requires further investigation. The topical application of capsaicin to the forearm in healthy volunteers in Study three failed to induce hyperalgesia in the ipsilateral forehead. It would be interesting to see whether inflammation of deeper tissue such as that induced by intramuscular capsaicin injection produces hemilateral hyperalgesia. As discussed earlier, carageenan injection in the rat hindpaw produced hyperalgesia not only in the injected hindpaw but also in the ipsilateral forepaw [36]. Furthermore, additional factors may contribute to the spread of hyperalgesia in CRPS as a large proportion of CRPS patients without ipsilateral forehead hyperalgesia to pressure-pain also reported swelling in their affected limb (Study seven). Such factors may involve mechanisms that become more prominent with the progression of the disease as CRPS patients with ipsilateral forehead hyperalgesia to pressure-pain reported a greater pain duration than patients without ipsilateral forehead hyperalgesia (Study seven).

3. Dysfunction in generalized and hemilateral pain control mechanisms, in particular to stimulation of the affected limb, may contribute to the hemilateral spread of sensory disturbances in CRPS.

As described in chapter 2, diffuse noxious inhibitory controls (DNIC) denote the mechanism by which a noxious stimulus reduces pain sensitivity at remote body sites [29]. This mechanism probably contributed to the bilateral reduction in pain sensitivity in the forehead of healthy volunteers during cold-induced limb pain (Study one and two) and capsaicin-induced inflammatory limb pain (Study three). In CRPS patients, noxious cold stimulation of the unaffected limb also reduced forehead sensitivity to pressure-pain (Study six), although the effect was weaker (delayed) than the reduction of forehead sensitivity in healthy volunteers (Study one). Interestingly, the DNIC effect did not appear to be evoked
during noxious cold stimulation of the affected limb in the CRPS patients (Study six). Thus the DNIC effect seems to be compromised in patients with CRPS, in particular to stimulation of the affected limb. This is consistent with previous findings that forehead cooling increases, rather than decreases, CRPS pain [11].

DNIC is served by a supraspinal loop with ascending and descending pathways in the ventrolateral quadrant and the dorsolateral funiculus respectively [9; 38]. As discussed in chapter 10, left-sided lesions of the ventrolateral quadrant in the cervical cord in animals reduced the remote inhibitory DNIC effect from stimulation of the right hindpaw whereas the activation of DNIC from stimulation of the left hindpaw was unaffected [38]. Thus DNIC related transmission in the afferent pathway from the affected limb (e.g., in the ipsilateral dorsal horn or the contralateral ventrolateral quadrant) could be disrupted in CRPS.

Both the spinothalamic tract (that relays nociceptive information to the cerebral cortex) and the spinoreticular tract involved in DNIC contain projections from wide dynamic range neurons in lamina V. A failure to inhibit activity in wide dynamic range neurons that receive input from the CRPS-affected limb could sensitize neurons in the thalamus or cerebral cortex that receive convergent information from hemilaterial body sites. As discussed in chapter 10, this could account for heightened sensitivity to stimulation of not only the affected limb but also areas outside the limb on the ipsilateral side of the body. A dysfunction in inhibitory control in CRPS could also unmask diffuse pain facilitation, thus promoting the further transfer of nociceptive messages to higher brain sites [3].

In healthy volunteers, the reduction in forehead sensitivity to pressure-pain during cold-induced limb pain was greater in the ipsilateral than contralateral forehead (Study one). Similarly, capsaicin-induced inflammatory limb pain was associated with a reduction
in pressure-pain sensations in only the ipsilateral forehead (Study three). This ipsilateral response was not seen in the forehead of CRPS patients during noxious cold stimulation of the affected or the unaffected limb (Study six). As discussed in chapter 5 and 7, noradrenergic activity emanating from the locus coeruleus (LC) may underlie the reduction of pain sensitivity in the ipsilateral forehead during cold-induced and capsaicin-induced limb pain in healthy volunteers. This mechanism could be compromised in CRPS patients.

Study five provided further indications of a dysfunction in inhibitory pain control from the LC in CRPS. Acoustic startle in the ipsilateral ear increased pain in the CRPS-affected limb more so than startle in the contralateral ear, and auditory discomfort was similarly greater to startle in the ipsilateral than contralateral ear suggestive of dysfunction in a mechanism that influences central processing hemilaterally. As the LC projects both to the cochlear nucleus in the auditory system and the dorsal horn in the spinal cord and has the potential to produce facilitation at both of these sites via actions at $\alpha_1$-adrenoeceptors [7; 17; 19; 22; 28; 33], a shift toward facilitation from the LC could explain the greater increase in CRPS to stimulation in the ipsilateral than the contralateral ear as well as the greater auditory discomfort to ipsilateral startle.

Serotonergic pain modulation from raphe nuclei such as the rostral ventromedial medulla (RVM) may also be compromised in CRPS patients. As mentioned in chapter 2, serotonergic projections from the RVM may have inhibitory or facilitatory actions depending on the receptors activated [32; 42]. Similar to the LC, raphe nuclei innervate the cochlear nucleus in addition to the dorsal horn [16; 42]. Thus a dysfunction in inhibitory control from this site could unmask generalized facilitation of activity both in the cochlear nucleus and dorsal horn neurons, and could explain the increase in CRPS pain to acoustic stimulation in both ears. The recent findings by Seifert et al. [34] that pain ratings to repetitive noxious electrical stimulation of both the affected and unaffected limb decreased
more slowly in CRPS patients than controls is consistent with a generalized dysfunction in inhibitory pain control.

Thus a number of central pain control mechanisms may be compromised in CRPS. A failure of these mechanisms to control the central transfer of nociceptive messages from the affected limb, and even more so a shift toward facilitation of such messages, may promote activity in wide dynamic range neurons that receive input from the CRPS-affected limb and ultimately contribute to sensitization of neurons in the thalamus or cerebral cortex. Hyperexcitability in thalamic nuclei contralateral to the affected limb which receive convergent input from hemilateral body sites could not only explain the presence of hemilateral hyperalgesia but could also explain heightened sensitivity to other forms of sensory input. Brain imaging studies have demonstrated hyperexcitability in somatosensory and motor cortices corresponding to the affected limb in CRPS [18; 23; 31; 37]. It would be interesting to determine whether a similar pattern exists in the auditory cortex.

The involvement of these pain control mechanisms in the generation and spread of hyperalgesia in CRPS should be explored further. Future studies could employ more invasive measures such as PET scans using radioactively-labeled neurotransmitters to assess changes in the central release of noradrenaline and serotonin following startle with a loud tone and noxious cold stimulation to confirm the involvement of such mechanisms. Attempts could also be made to disrupt such mechanisms in healthy volunteers to determine whether this evokes a spread of hemilateral sensory disturbances. Study two attempted to do this by employing optokinetic stimulation. However, this did not appear to be an adequate procedure for doing so. Instead the pharmacological administration of drugs such as the opioid receptor antagonist naltrexone, the α₂-adrenoceptor antagonist yohimbine, or the benzodiazepine valium, which enhances the effects of GABA thereby reducing the central release of noradrenaline and serotonin, could be employed in an
Fig. 1. **Ascending pain pathway from the CRPS limb and coeruleospinal pain modulation.** Heightened nociceptive input from the CRPS limb (red) may produce hyperexcitability both in the dorsal horn (DH) and the contralateral thalamus (TH) in patients with CRPS. A disruption of descending inhibitory control from the locus coeruleus (LC) (purple) may unmask the further facilitation of neurons in the ipsilateral dorsal horn. In addition a shift toward facilitatory control from the LC may facilitate neurons in the ipsilateral trigeminal nucleus caudalis (TNC) that transmit nociceptive messages from the forehead to the thalamus (blue), and may also facilitate neurons in the ipsilateral cochlear nucleus (CN) that transmit auditory impulses from the ipsilateral ear to thalamic nuclei (green). This could explain the heightened sensitivity both to sensory and auditory stimuli on the symptomatic side of the body in CRPS. The convergence of these stimuli in an already hyperexcitable thalamus may also explain such findings. The shift from inhibitory to facilitatory pain control in diffuse bidirectional pain control mechanisms such as diffuse noxious facilitatory versus diffuse noxious inhibitory controls or serotonergic projections from raphe nuclei may explain findings of generalized sensory disturbances in CRPS patients. For clarity, descending influences from the LC are presented schematically.
attempt to block mechanisms such as stress-induced analgesia, coeruleospinal and DNIC pain control. Such studies may also help shed light on whether the lack of inhibitory control or presence of facilitatory control is a preemptive factor in the development of CRPS or a consequence of the condition. Forehead sensitivity was generally symmetrical in healthy volunteers, but ipsilateral forehead hyperalgesia to pressure-pain or sharpness was present in a minority of healthy volunteers. It is tempting to speculate that disturbances in the central processing of nociceptive input could mediate such effects and could be a predisposing factor for the development of CRPS. Findings that some patients develop recurrent episodes of CRPS sometimes in a different limb [1; 2; 24] similarly suggest that something may predispose certain individuals to develop this condition. Exaggerated neurogenic inflammation has also been proposed as a predisposing factor for the development of CRPS as enhanced reflex vasodilatation was present in former CRPS patients [30]. Exaggerated neurogenic inflammation could sensitize peripheral and central neurons and activate facilitatory mechanisms, or perhaps inhibitory pain control mechanisms become fatigued over time unmasking facilitatory control.

In conclusion, the findings presented in this thesis suggest that heightened nociceptive traffic in the CRPS-affected limb may contribute to heightened sensitivity both in the CRPS affected limb and the ipsilateral forehead by inducing sensitization in spinal and supraspinal pathways subserving the affected limb. This hypothesis is presented in Figure 1. In particular, sensitization of the contralateral thalamus, which receives convergent input from hemilateral body sites, could explain the hyperalgesia at various body sites ipsilateral to the affected limb. In CRPS, this process may be further exacerbated by a failure of central pain control mechanisms to inhibit nociceptive activity in the spinal cord. More importantly, a shift toward facilitatory control in pain control mechanisms, with a bidirectional role such as the noradrenergic actions from the LC, the serotonergic actions
from raphe nuclei or diffuse noxious facilitatory versus inhibitory controls [3; 19; 22; 41; 42], may promote the further facilitation of nociception. The facilitation of more generalized mechanisms could explain reports by some researchers that sensations are also more generally disturbed in patients with CRPS [20; 35].


## Appendix A

### Patient participation in Study four, five, six and seven

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<th>Study five</th>
<th>Study six</th>
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