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

Lone Knudsen

BA (Hons) (Psych)

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

July 2009

School of Psychology, Murdoch University, Western Australia
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.


Lone Knudsen

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 carageenan-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 hemilateral 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.
# Table of contents

Abstract iii  
Publications x  
Author contributions xi  
Acknowledgements xii  
List of tables xvi  
List of figures xix  

1.0 Introduction to complex regional pain syndrome  
   1.1 The problem of complex regional pain syndrome 1  
   1.2 Diagnosis and clinical features 2  
      1.2.1 Pain and sensory disturbances 5  
      1.2.2 Vasomotor disturbances 6  
      1.2.3 Sudomotor disturbances/edema 6  
      1.2.4 Motor/trophic disturbances 7  
   1.3 Spread of symptoms 8  

2.0 Normal pain processing  
   2.1 Pain and its function 22  
   2.2 Nociception 22  
      2.2.1 Peripheral nociception 22  
      2.2.2 Central nociception 23  
      2.2.3 Pain modulation mechanisms 25
3.0 CRPS pathology

3.1 Peripheral pathology  53

3.1.1 Peripheral sensitization and exaggerated inflammation  53

3.1.2 Sympathetic nervous system dysfunction  55

3.2 Central pathology  57

3.2.1 Central sensitization  57

3.2.2 Central disinhibition  58

3.2.3 Cortical changes  59

3.3 Psychological factors  60

3.4 Conclusion from introductory chapters 1, 2 and 3  61

4.0 Approach  

4.1 The studies  76

5.0 Cold-induced limb pain decreases sensitivity to pressure-pain sensations in the ipsilateral forehead  

5.1 Study one  81

6.0 Effect of limb pain and motion sickness on scalp tenderness  

6.1 Study two  113

7.0 Limb inflammation produces analgesia to pressure-pain in the ipsilateral forehead of healthy volunteers  

7.1 Study three  142

xiv
8.0 Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine
   8.1 Study four 172

9.0 Ipsilateral auditory startle enhances hyperacusis and limb pain in complex regional pain syndrome
   9.1 Study five 209

10.0 Failure of inhibitory pain modulation to noxious stimulation of the symptomatic limb, but not the healthy limb, in complex regional pain syndrome
   10.1 Study six 238

11.0 Hemilateral pressure hyperalgesia: a specific sign in complex regional pain syndrome?
   11.1 Study seven 269

12.0 Conclusions
   12.1 Summary of the seven studies 297
   12.2 Implication for CRPS 300

Appendix A 314
List of tables

Tables from Chapter 1.0

Table 1  IASP diagnostic criteria for CRPS (criteria 2–4 must be satisfied) [61]  2

Table 2  Proposed CRPS diagnostic criteria [40; 45]  4

Tables from Study one

No tables

Tables from Study two

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  135

Table 2  Pearson’s correlations between changes in forehead sensitivity after OKS and the development of motion sickness  136

Tables from Study three

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  167
### Tables from Study four

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sensory, vasomotor/sudomotor and motor/trophic disturbances in CRPS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 2</td>
<td>Sensory thresholds and allodynia in the symptomatic and healthy limbs before ketamine and placebo creams were applied to the symptomatic limb</td>
</tr>
<tr>
<td>Table 3</td>
<td>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</td>
</tr>
<tr>
<td>Table 4</td>
<td>Association (Spearman’s rank-order correlation coefficient) between sensory disturbances in the symptomatic limb and asymmetry of sensations in the forehead</td>
</tr>
</tbody>
</table>

### Tables from Study five

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sensory, vasomotor/sudomotor and motor/trophic disturbances in CRPS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 2</td>
<td>Association (Spearman’s rank-order correlation coefficient) between sensory disturbances in the affected limb and asymmetry of sensations in the forehead</td>
</tr>
<tr>
<td>Table 3</td>
<td>Demographic and sensory characteristics in startle-responders and non-responders</td>
</tr>
<tr>
<td>Table 4</td>
<td>Association (Spearman’s rank-order correlation coefficient)</td>
</tr>
</tbody>
</table>
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 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

Tables from Study six

Table 1
Sensory, vasomotor/sudomotor and motor/trophic disturbances in CRPS patients

Tables from Study seven

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 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
List of figures

Figures from Study one

Figure 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.

Figure 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.

Figure 3  Hand pain and distress ratings for 12 minutes after the 2 °C. Error bars represent standard errors and the arrow represents the CP.

Figure 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.

**Figure 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.

**Figure 6** Hand pain and distress ratings after each 4 °C immersion. Error bars represent standard errors.

**Figure 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.

**Figures from Study two**

**Figure 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.
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.

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.

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 (** p < 0.01) but no change was seen in the pain insensitive group. After the OKS, sharpness ratings increased in both groups (*** p < 0.001), but decreased immediately after the CP in the pain sensitive group (*** p < 0.001) with a further decrease 2 min later (** 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 (*** p< 0.001). Error bars represent standard errors.

**Figures from Study three**

**Figure 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.

**Figure 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.

**Figure 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.
errors and the arrow represents the initial application of capsaicin.

Figure 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.

Figures from Study four

Figure 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).

Figure 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).

Figure 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).

Figure 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.

Figures from Study five

Figure 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.

Figures from Study six

Figure 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.

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.

**Figure 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.

**Figure 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.

*Figures from Study seven*

**Figure 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).

**Figure 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.
Figure 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.

Figures from Chapter 12.0

Figure 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.