The Specificity and Mechanisms of Hemilateral Sensory Disturbances in Complex Regional Pain Syndrome

Lone Knudsen,* Philip M. Finch,* † and Peter D. Drummond*

*School of Psychology, Murdoch University, Perth, Western Australia.
†Perth Pain Management Centre, Perth, Western Australia.

Abstract: Hyperalgesia often extends from the affected limb to the ipsilateral forehead in patients with complex regional pain syndrome (CRPS). To investigate whether this is more common in CRPS than other chronic pain conditions, pressure-pain thresholds and sharpness 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 in 32 patients with chronic pain other than CRPS (neuropathic or nociceptive limb pain, radicular pain with referral to a lower limb or postherpetic neuralgia), and in 34 patients with CRPS. Ipsilateral forehead hyperalgesia to pressure pain was detected in 59% of CRPS patients compared with only 13% of patients with other forms of chronic pain. Immersion of the CRPS-affected limb in painfully cold water increased forehead sensitivity to pressure, especially ipsilaterally, whereas painful stimulation of the healthy limb reduced forehead sensitivity to pressure pain (albeit less efficiently than in healthy controls). In addition, auditory discomfort and increases in pain in the CRPS-affected limb were greater after acoustic startle to the ear on the affected than unaffected side. These findings indicate that generalized and hemilateral pain control mechanisms are disrupted in CRPS, and that multisensory integrative processes may be compromised.

Perspective: The findings suggest that hemilateral hyperalgesia is specific to CRPS, which could be diagnostically important. Disruptions in pain-control mechanisms were associated with the development of hyperalgesia at sites remote from the CRPS limb. Addressing these mechanisms could potentially deter widespread hyperalgesia in CRPS.

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Key words: Complex regional pain syndrome, spread of sensory disturbances, pain laterality, endogenous pain control, DNIC.

Complex regional pain syndrome (CRPS) is associated with hyperalgesia to static pressure in the forehead ipsilateral to the affected limb.12 This may have important diagnostic and pathophysiologic implications, as it suggests that central disturbances in nociceptive processing contribute to CRPS.

The aims of the present study were to investigate the specificity of this symptom and to explore links with nociceptive responses to startle stimuli9,13 and disrupted inhibitory pain control in CRPS.29 As pain may compromise sensory processing hemilaterally in CRPS,30,31,34 it was hypothesized that painful stimulation of the CRPS-affected limb would aggravate pressure hyperalgesia in the ipsilateral forehead. It was further hypothesized that limb pain and auditory discomfort would be greater when a startle stimulus was presented on the CRPS-affected rather than the unaffected side, and that heightened pain to the ipsilateral startle stimulus would be linked with pressure hyperalgesia in the ipsilateral forehead.

Methods

The procedures were approved by the University Ethics Committee. Each participant provided informed consent and remained on stable routine medication (analgesics, anticonvulsants and/or antidepressants). The first study was run in a standard medical setting and the second and third experiments were carried out in a laboratory maintained at 20 ± 2°C. The CRPS sample consisted of patients with unilateral limb pain who met diagnostic25 and research criteria16 for CRPS type 1 (36 patients) or
**Experiment 1: Prevalence of Sensory Disturbances in the Forehead**

Eight patients with postherpetic neuralgia on 1 side of the trunk, 6 with posttraumatic neuropathic limb pain, and 11 with nociceptive limb pain (osteoarthritis, 2 tendinosis, and 1 thrombophlebitis) were recruited from local hospitals and pain clinics. Another 7 patients had radicular pain with diffuse referral to the lower limb (3 patients) or pain localized to the knee (1 patient), thigh (2 patients) or lumbar region (1 patient). In the CRPS group, 17 had upper limb pain and another 17 had lower limb pain (supplementary Table 1). Medication status generally did not differ between patients with and without CRPS, although fewer patients with radicular pain were medicated (supplementary Table 2).

Pressure-pain thresholds (PPT) and sharpness to stimulation with a firm bristle were assessed on each side of the forehead and at the site of pain.15 The dorsal hand or foot was assessed in limb-pain patients. In patients with radicular pain, sensations were assessed in the lumbar spinal region, whereas an affected region on the upper back or chest was usually the site of testing in patients with postherpetic neuralgia. 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) in 80-g increments to the forehead and 200-g increments elsewhere until participants reported pain or to a maximum of 2.3 kg. Only 9 patients tolerated the maximum pressure, usually at the unaffected site. 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) which was applied until it bent for 1 second. This was tolerated by all patients.

**Experiment 2: Effects of Cold Pressor Stimulation on Ipsilateral Forehead Hyperalgesia in CRPS**

Twenty-two CRPS patients participated in this study (supplementary Table 1). The cold pressor test involved sequential immersion of the CRPS-affected limb and the contralateral healthy limb in circulating water maintained at 2 ± 1°C for 1 minute.21 If the participant could not tolerate this temperature, 10°C was used. The patient reported pain and distress verbally from 0 (none) to 10 (extremely severe) 30 seconds into the immersion. The dorsal hand or foot was assessed in limb-pain patients. In half of the patients, the CRPS-affected limb was immersed first. At least 15 minutes elapsed between the 2 immersions. Before and after each cold pressor test, PPT and sharpness were assessed on each side of the forehead using the procedures described in Experiment 1. These measures were repeated at 2-minute intervals for 12 minutes.21

**Experiment 3: Effect of an Acoustic Startle Stimulus on Pain in the CRPS-Affected Limb**

The sample consisted of 28 patients with CRPS (supplementary Table 1). PPT and sharpness were measured on each side of the forehead using the procedures described in Experiment 1. Loud tones (100 Hz, 102 dB(A), 5-second duration) were delivered to each ear through headphones. Participants rated pain intensity on a scale from 0 (no pain) to 10 (extremely severe pain),13 and rated auditory discomfort on a scale from 0 (not unpleasant) to 10 (extremely unpleasant). The tone was presented 4 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 tone was presented on the CRPS-affected side in 50% of participants. Pain in the CRPS-affected limb was rated every 5 seconds for 15 seconds before and for 30 seconds after each tone. Patients were warned about the appearance of the tone to reduce any painful effect of sudden movement.

**Statistical Approach**

Fisher’s exact test or chi-square tests were used to analyze nominal data, and the Mann-Whitney test or Wilcoxon’s matched-pairs signed-ranks test were used to analyze ordinal data. In general, hypotheses that involved repeated measures were investigated with analysis of variance and, where appropriate, significant effects were investigated further with the least significant difference test. The Huynh-Feldt epsilon was used to correct for violations of sphericity. Although analysis of variance is robust to violations of normality, Wilcoxon’s test was employed to investigate significant interactions in instances where data did not fit a normal bell-shaped curve. Data are reported as mean ± S.E. The criterion of statistical significance was \( P < .05 \).

**Results**

**Experiment 1: Prevalence of Sensory Disturbances in the Forehead**

In preliminary tests in patients without CRPS, neither the pain location nor type of pain influenced sensory asymmetry in the forehead (supplementary Fig 1). Therefore, patients without CRPS were grouped together to compare Forehead Side (ipsilateral or contralateral to the affected area) \( \times \) Pain Group (with or without CRPS) on PPT and sharpness in the forehead.

The PPT was lower on the ipsilateral than contralateral side of the forehead in patients with CRPS (497 ± 48 g versus 648 ± 43 g, \( P < .01 \)) but not in patients without CRPS (693 ± 47 g versus 703 ± 44 g, difference not significant) [Forehead Side \( \times \) Pain Group interaction \( F(1,64) = 8.09, P < .01 \)]. Sharpness to punctate stimulation was greater on the ipsilateral than contralateral side of the forehead in both groups of patients [mean rating 3.6 ± .3 versus 2.6 ± .2, \( F(1,64) = 9.00, P < .01 \)]. In addition, sharpness was greater on both sides of the forehead in patients with than without CRPS [3.6 ± .3 versus 2.6 ± .3, \( F(1,64) = 6.12, P < .05 \)].
Findings in patients were compared with findings in 96 pain-free women and 45 pain-free men (mean age = 24.0 ± .6 years) examined by the authors previously. In the pain-free group, the difference in the PPT between the left and right sides of the forehead was less than 160 g in 80% of cases, and sharpness ratings differed by 2 points or less in 90% of cases. When these values were used to define the normal range of asymmetry in forehead sensitivity, ipsilateral forehead hyperalgesia to pressure pain was detected in 59% of CRPS patients compared with only 13% of patients without CRPS \( \chi^2(1) = 15.29, P < .001 \). CRPS patients with this symptom were older and had suffered pain longer than the remainder of CRPS patients, but there were no differences between women and men (supplementary Table 3).

Ipsilateral forehead hyperalgesia to pressure pain was identified in 65% of patients with upper-limb pain and in 53% of patients with lower-limb pain (difference not significant). Ipsilateral forehead hyperalgesia to sharpness was detected in 38% of CRPS patients and 28% of patients without CRPS (difference not significant).

**Experiment 2: Effects of Cold Pressor Stimulation on Ipsilateral Forehead Hyperalgesia in CRPS**

Before the immersion, patients reported moderate pain in their CRPS-affected limb (mean rating 5.1 ± .6 on a 0 to 10 scale), and pain-related distress averaged slight to moderate (mean rating 3.5 ± .7). Only 7 patients tolerated the 2°C water for their CRPS-affected limb while all but 3 patients tolerated this temperature for the contralateral healthy limb. Nonetheless, pain in the CRPS-affected limb was similar to pain in the healthy limb during the immersions (mean rating 8.1 ± .5 versus 7.9 ± .6). Pain in the CRPS-affected limb decreased during immersion of the healthy limb (from 5.3 ± .6 to 3.8 ± .7, \( P < .05 \)) but returned to preimmersion levels immediately afterwards.

The PPT was lower on the ipsilateral than contralateral side of the forehead throughout the experiment (Fig 1) \( \text{IF}(1,21) = 9.04, P < .01 \). After immersion of the healthy limb, the PPT fell briefly on both sides of the forehead but then increased to a maximum 10 minutes later (Fig 1A). In contrast, immersion of the CRPS-affected limb evoked an immediate bilateral decrease in PPT which persisted for the remainder of the assessments (Fig 1B) \( \text{Time} \times \text{Immersion} \) (CRPS-affected limb versus healthy limb) \( F(4.12, 86.57) = 2.87, P < .05 \). Importantly, forehead asymmetry increased after immersion of the CRPS-affected limb (from 55 ± 35 g lower on the CRPS-affected side to 132 ± 39 g lower on this side after the immersion, \( P < .05 \)), but did not change after immersion of the healthy limb. Sharpness was symmetrical in the forehead during each limb immersion and did not change after the immersions (Figs 1C and 1D).

**Experiment 3: Effect of an Acoustic Startle Stimulus on Pain in the CRPS-Affected Limb**

Auditory discomfort and increases in limb pain were greater when the startle stimulus was presented on the CRPS-affected side than on the unaffected side (Table 1). Greater auditory discomfort on the CRPS-affected side was associated with greater hyperalgesia to pressure (\( r = .53, P < .01 \)) and sharpness (\( r = .46, P < .05 \)) on the ipsilateral side of the forehead. However, changes in limb pain were unrelated to hyperalgesia in the ipsilateral forehead.

**Discussion**

Hyperalgesia to pressure pain in the ipsilateral forehead was more prevalent in upper- and lower-limb CRPS than in other forms of chronic pain, and was associated with altered pain control. These findings suggest that ipsilateral forehead hyperalgesia is specific to CRPS, and that an ipsilateral deficit in pain control may contribute to CRPS.

**Ipsilateral Forehead Hyperalgesia in CRPS**

Sensitivity to various forms of stimulation (generally pressure pain, but occasionally also cold pain, heat pain, sharpness, and allodynia to brushing) is elevated on the ipsilateral side of the forehead in CRPS. This may become more prominent with progression of the disease, as we found that CRPS patients with ipsilateral forehead hyperalgesia to pressure pain were older and reported a longer duration of pain than the other CRPS patients. The hyperalgesia is not merely an effect of local limb pain, as limb pain suppresses pressure-pain sensations in the ipsilateral forehead of healthy volunteers. Moreover, we found that PPT were symmetrical in the forehead of most chronic pain patients without CRPS. Thus, ipsilateral forehead hyperalgesia may be important diagnostically for CRPS. Sharpness was elevated on the ipsilateral side of the forehead in both groups but was greater in patients with rather than without CRPS, consistent with central sensitization and/or failure of inhibitory pain modulation mechanisms.

Noxious stimuli reduce pain sensitivity at remote body sites. This effect of diffuse noxious inhibitory controls (DNIC) probably contributed to an immediate robust bilateral reduction in pain sensitivity in the forehead of healthy volunteers during cold-induced limb pain in a previous study. In the present case, pain decreased briefly in the CRPS-affected limb when the contralateral limb was immersed in painfully cold water. In addition, sensitivity to pressure pain decreased weakly on both sides of the forehead several minutes after the healthy limb was immersed. However, immersion of the CRPS-affected limb did not reduce forehead sensitivity; instead, sensitivity to pressure pain increased on both sides of the forehead despite intense limb pain. Why sharpness did not show a similar trend is uncertain, but the dissociation is consistent with reports that pain of deep and superficial origin is processed at different cortical and subcortical sites.

Although the healthy limb was more commonly immersed in 2°C water than the CRPS-affected limb, temperature differences are unlikely to account for the present findings as immersion of the
limbs was equally painful. Thus, it seems likely that bilateral pain-inhibitory influences mediated by DNIC were disrupted in our patients. In contrast, DNIC was enhanced by noxious stimulation of the painful limb in monoarthritic, polyarthritic, and peripheral mononeuropathic animals, and was evoked by innocuous stimulation of an area of static allodynia in patients with peripheral nerve injury.

We reported previously that limb pain evoked a greater reduction in sensitivity to pressure pain on the ipsilateral rather than the contralateral side of the forehead in healthy volunteers. However, the opposite trend was seen during immersion of the CRPS-affected limb, suggesting that a hemilateral pain-modulation mechanism (perhaps involving brainstem nuclei such as the locus coeruleus or raphe nuclei) had been compromised. Consistent with this possibility, both auditory discomfort and increases in pain in the CRPS-affected limb were greater after an acoustic startle stimulus on the affected rather than the unaffected side. In contrast, acoustic startle stimuli inhibit pain in controls. Inhibitory and excitatory influences that project from the locus coeruleus and raphe nuclei to the cochlear nuclei (the first link in the neural pathway of the acoustic startle response), and to nociceptive neurons in thalamus and dorsal horn, could mediate auditory discomfort and associated limb pain. Alternatively, hyperacusis in CRPS could involve convergence of auditory input onto sensitized nociceptive neurons in subcortical or cortical centers, as auditory discomfort was associated with hyperalgesia in the CRPS-affected limb in a previous study and with hyperalgesia to pressure pain and sharpness on the ipsilateral side of the forehead in the present study.

**Table 1. Auditory Discomfort and Increases in Limb Pain to the Startle Stimulus**

<table>
<thead>
<tr>
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<th>Ipsilateral Startle</th>
<th>Ipsilateral Startle</th>
<th>t-test</th>
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<tbody>
<tr>
<td>Auditory discomfort*</td>
<td>5.8 ± 0.5</td>
<td>5.0 ± 0.5</td>
<td>2.55</td>
</tr>
<tr>
<td>Increase in limb pain†</td>
<td>0.74 ± 0.14</td>
<td>0.34 ± 0.12</td>
<td>5.87</td>
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</tbody>
</table>

*Unpleasantness rating on a 0 to 10 verbal rating scale.
†Limb pain was rated on a 0 to 10 verbal rating scale every 5 seconds for 15 seconds before and 30 seconds after the startle stimulus. The increase in limb pain represents the mean difference in pain ratings from before to after the startle stimulus.

**Methodological Issues**

Due to the demographic features of CRPS, more women were in the CRPS group than in other diagnostic categories. In addition, CRPS patients generally were younger than other patients. However, these characteristics did not appear to influence the outcome as ipsilateral forehead hyperalgesia was detected in a similar proportion of men and women, and patients with this...
symptom were older, not younger, than other patients. Nonetheless, as the investigator was aware of patients’ diagnoses, blinded studies are required to confirm the present observations. Another limitation is that most patients were medicated. However, it is difficult to envision how analgesic, antidepressant, or anticonvulsant medication could enhance pain or hyperalgesia to cold water immersions or startle stimuli, or evoke asymmetric hyperalgesia in the forehead.

**Clinical Implications**

From a diagnostic perspective, hyperalgesia in the ipsilateral forehead could help to distinguish CRPS from other forms of chronic limb pain. Our findings also suggest that a failure of endogenous pain control, or a shift toward pain facilitation, contributes to hemilateral hyperalgesia in CRPS. Together with chronic inflammation and hyperalgesia in the CRPS-affected limb, disturbances in central nociceptive processing may contribute to the sensitization of supraspinal nociceptive neurons in CRPS. Somatosensory, auditory, visual, and emotional inputs may then aggravate pain by feeding into this sensitized nociceptive network.

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**Supplemental Data**

Supplementary data accompanying this article is available online at www.jpain.org and www.sciencedirect.com. The supplementary data include Supplementary Tables and Figure.

**References**


