A disturbance in sensory processing on the affected side of the body increases limb pain in complex regional pain syndrome

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Abstract

Objectives. The aim of this study was to determine whether a central disturbance in somatosensory processing contributes to limb pain in complex regional pain syndrome.

Methods. In 37 patients with complex regional pain syndrome, the effect of cooling the ipsilateral forehead on pain in the affected limb was compared with the effect of cooling the contralateral forehead. In addition, symptoms associated with cold-evoked limb pain were explored.

Results. Limb pain generally increased when the ipsilateral side of the forehead was cooled but did not change when the contralateral side of the forehead was cooled. Increases were greatest in patients with heightened sensitivity to cold, brushing and pressure-pain in the ipsilateral forehead, in patients with heightened sensitivity to pressure-pain in the limbs, and in patients with chronic symptoms. In contrast, sensitivity to light touch was diminished in the CRPS-affected limb of patients whose limb pain remained unchanged or decreased during ipsilateral forehead cooling.

Conclusions. These preliminary findings suggest that a central disturbance in sensory processing and pain modulation, which extends beyond the affected limb to the ipsilateral forehead, contributes to symptoms in a subgroup of patients with complex regional pain syndrome.

Key words: complex regional pain syndrome; forehead cooling; ipsilateral pain modulation; locus coeruleus

Introduction

Complex regional pain syndrome (CRPS) typically develops after injury to a limb, with or without obvious nerve trauma. Patients usually describe a burning sensation that is aggravated by movement, the limb being touched, cold environments, emotional arousal, and startle stimuli. The pain is associated with motor deficits and autonomic disturbances; the limb swells, sweats excessively, and is warmer or cooler than the unaffected limb.[1] Regional inflammation contributes to sensory and autonomic disturbances in the acute stage of CRPS, stemming from the actions of pro-inflammatory mediators such as tumor necrosis factor-α.[2] In chronic CRPS, loss of nutritive blood flow and accumulation of oxygen-derived free radicals may result in tissue damage.[2] As well, in a subgroup of patients, venous noradrenaline and its metabolites are depleted,[3,4] the density of α_1-adrenoceptors is increased,[5] and blood vessels[6] and nociceptive afferents[7] are supersensitive to adrenergic agents.

In addition to these peripheral disturbances, changes in pain processing within the central nervous system may result in the spread of pain and other sensory disturbances from the initial site of injury to other parts of the limb and elsewhere in the body.[8-10] The ipsilateral spread of hyperalgesia could have pathophysiological implications as it is more common in CRPS than in other chronic unilateral pain syndromes.[9] However, the underlying mechanism is unknown.

Cold-pain in the forehead suppresses limb pain in healthy controls, presumably through the actions of diffuse noxious inhibitory controls, but augments pain in the affected limb of CRPS patients.[11] We reasoned that limb pain evoked by cooling the ipsilateral forehead, coupled with heightened sensitivity to sensory stimulation in this region, may indicate that sensory processing and pain modulation are altered on the affected side of the body in CRPS. Alternatively, cooling the forehead may trigger adrenergic activation of

nociceptive afferents in the affected limb (e.g., at the site of peripheral nerve injury in patients with CRPS type II). If so, cooling either side of the forehead cooling might generate limb pain. To investigate this in the present study, the effect of cooling each side of the forehead on limb pain was assessed in patients with CRPS type I or II, and symptoms associated with cold-evoked limb pain were explored.

Methods

Participants

Eight men and 29 women aged between 19 and 67 years met proposed Budapest clinical criteria for CRPS type I (29 participants) or type II (eight participants).[12] Each patient provided written informed consent for the procedures, which were approved by the institutional ethics committee.

Procedures

To assess effects of forehead cooling on limb pain, the 1.5 cm diameter end of a 10 cm metal cylinder cooled to 2^{o}C was applied sequentially to each side of the forehead for 30 s while the patient rated limb pain at 5-s intervals (0 corresponded to "no pain" and 10 to "extremely intense pain"). The CRPS side was tested first on 50% of occasions. Tests were separated by 1-2 min to allow pain to subside, and were interspersed randomly among the sensory tests described below. In two patients with bilateral limb pain, the CRPS side was defined as the more severely affected side.

Pressure-pain thresholds (PPTs) and sensitivity to cold and sharpness were assessed on the medial and lateral aspects of the dorsum of the CRPS-affected and contralateral hands or feet and in the supraorbital region on each side of the forehead. In addition, patients reported whether lightly brushing the limbs or forehead with a soft paintbrush (3 mm diameter contact area, approximate bending force of the combined bristles 10 g) provoked an abnormal sensation (e.g., pins-and-needles, prickling, tingling, a rough or sharp sensation, or

pain). PPTs were established with a purpose-built spring-loaded algometer (1 cm diameter hemispheric tip). The pressure was applied in 250 g increments to the limbs and 100 g increments to the forehead until the patient reported pain or to 2.5 kg. To assess sensitivity to cold, the patient was asked to rate coldness between 0 (not cold at all) and 10 (extremely cold) after the end of the 2^{o}C bar was applied for 7 s. Sharpness was rated between 0 (not sharp) and 10 (stabbing) in response to bending a nylon bristle at each site for 1 s (bending force 10 g). In addition, patients rated sharpness after the bristle had been applied another four times at the same site at 1 s intervals. Tactile, heat-pain and cold-pain thresholds were assessed on the dorsum of the CRPS-affected and contralateral hands or feet. To detect heat- and cold-pain thresholds, the temperature of a thermode (2 cm diameter) increased or decreased 0.5^{o}C/s from a neutral starting temperature until the patient reported pain. To detect tactile thresholds, graded nylon monofilaments (Senselab von Frey Aesthesiometer, Somedic Sales AB, Horby, Sweden) were applied to the medial and lateral aspects of the dorsum of the CRPS-affected and contralateral hands or feet at 5-10 s intervals. Patients closed their eyes throughout the procedure and reported when and where they noticed a sensation. The sequence started with filament 8 (nominal bending force 600 mg, 0.23 mm diameter) which was applied in random order to one of the four test sites. Sufficient force was applied to bend the filament for 1 s. Stronger or weaker filaments were then used as required, until the detection threshold was established for each site. Below threshold, the stimulus was missed on at least two of three trials. For all stimulus modalities, an average score was later calculated for each limb.

Statistical approach

Changes in limb pain during forehead cooling were investigated in a Side (ipsilateral or contralateral to the painful limb) by Time (before versus during cooling) analysis of variance. Clinical characteristics associated with changes in limb pain were explored in

analyses of variance, Fisher's exact two-tailed test and Student's t-tests. Results are reported as mean ± standard error, and the criterion of statistical significance was $p<0.05$.

Results

In the group as a whole, increases in pain in the CRPS-affected limb were greater when the ipsilateral than contralateral side of the forehead was cooled [$F(1,36) = 7.04$, $p<0.05$] (Figure 1). In addition, paraesthesiae (N = 6) and/or muscular sensations (tightening, cramps or involuntary movements of the affected limb; N = 7) sometimes developed when the ipsilateral forehead was cooled.

Individual differences in the response to ipsilateral forehead cooling

Twenty-one of the 37 patients (57%) reported that limb pain increased when the ipsilateral forehead was cooled, whereas limb pain did not change (12 patients, 32%) or decreased (4 patients, 11%) in the remainder of patients (Table 1). In preliminary analyses, clinical characteristics were similar in patients whose limb pain remained unchanged or decreased during ipsilateral forehead cooling. Therefore, these patients were combined into a single group (the comparison group) to determine whether they differed on certain clinical characteristics from patients who reported increases in limb pain during ipsilateral forehead cooling (the target group).

Sensory disturbances in the forehead. Sensitivity to cold and pressure was greater on the ipsilateral than contralateral side of the forehead in the target group, but was similar on both sides of the forehead in the comparison group [for cold ratings, Group x Side interaction $F(1,35) = 5.60$, $p<0.05$; for PPT, Group x Side interaction $F(1,34) = 15.3$, $p<0.001$] (Figure 2A and 2B). Sensitivity to single and multiple applications of a sharp stimulus was greater on both sides of the forehead in patients the target group than in patients in the comparison group [for a single application, main effect for Group $F(1,27) = 7.55$, $p<0.05$; for multiple applications, main effect for Group $F(1,27) = 6.88$, $p<0.05$] (Figure 2C and 2D). As well,

brushing the ipsilateral forehead provoked abnormal sensations in 10 of 21 patients in the target group (48%) compared with only one of 14 patients in the comparison group (7%) ($p<0.05$, Fisher's exact test).

Sensory disturbances in the limbs. Tactile thresholds to von Frey hairs were elevated in the CRPS-affected limb of patients in the comparison group but were similar in each limb of patients in the target group [Group x Side interaction $F(1,30) = 8.73$, $p<0.01$] (Figure 3). Sensitivity to cold, pressure and sharp stimulation was greater in the CRPS-affected than contralateral limb in both groups [for cold ratings, $F(1,34) = 16.3$, $p<0.001$; for cold-pain thresholds, $F(1,26) = 10.03$, $p<0.01$; for PPT, $F(1,34) = 53.3$, $p<0.001$; for a single sharp stimulus, $F(1,29) = 5.45$, $p<0.05$; for multiple sharp stimuli, $F(1,28) = 14.2$, $p<0.01$], with a trend for sensitivity to be greater in the CRPS-affected limb of the target than comparison group (Figure 4). In addition, PPTs were lower in both limbs of patients in the target than comparison group [main effect for Group $F(1,34) = 8.54$, $p<0.01$] (Figure 4D), and pain ratings before forehead cooling were greater the CRPS-affected limb of patients in target than comparison group [5.6 ± 0.4 versus 4.9 ± 0.3, $t(35) = 2.56$, $p<0.05$]. However, the proportion of patients who reported an abnormal sensation to brushing the CRPS-affected limb was similar in the target and comparison groups (86% and 87%, respectively).

Clinical features. Additional clinical characteristics (age, sex, duration of CRPS, medications) were compared between the two groups of patients with Student t-tests and Fisher's exact two-tailed test. Pain duration was greater in the target group than in the comparison group [66 ± 14 months for patients whose limb pain increased during ipsilateral forehead cooling versus 27 ± 9 months for patients whose limb pain decreased or remained unchanged, $t(35) = 2.16$, $p<0.05$], but age was similar in both groups (45 ± 2 years versus 49 ± 3 years, not significant). Three of 21 patients in the target group were male compared with 5 of 16 patients in the comparison group (difference not significant). The proportion of

patients with upper limb pain (43% versus 44%) was similar in the two groups, as was the proportion taking anticonvulsants (67% versus 75%), antidepressants (33% versus 13%), and opioid analgesics (38% versus 25%). Three patients in the target group (14%) and five patients in the comparison group (31%) had CRPS type II (difference not significant).

Discussion

In a subgroup of patients with CRPS, pain increased in the affected limb when the ipsilateral forehead was cooled. These patients were characterized by the chronicity and intensity of CRPS, by heightened sensitivity to stimulation of the forehead, particularly on the ipsilateral side, and by sensitivity to pressure-pain in the limbs. Taken together, these findings suggest that disturbances in sensory processing and pain modulation on the affected side of the body may contribute to symptoms in a subgroup of patients with chronic CRPS.

Limb pain ordinarily evokes *analgesia* to pressure-pain in the ipsilateral forehead of healthy participants.[13-15] Thus, *hyperalgesia* to painful pressure in the ipsilateral forehead of patients with a painful arm or leg implies disruption of an inhibitory ipsilateral pain modulation mechanism. One such system involves noradrenergic projections from the locus coeruleus which modulate nociceptive activity ipsilaterally in the spinal and medullary dorsal horn and that, when disrupted, contribute to neuropathic pain.[16-19] Although inhibitory effects generally predominate, this noradrenergic modulatory system may exert bidirectional influences on pain.[20-22] A shift toward pain facilitation in the spinal or rostral projections of this system might not only explain heightened sensitivity to pressure-pain and other sensations in the ipsilateral forehead but could also account for heightened pain in the CRPS-affected limb during forehead cooling and other forms of ipsilateral sensory stimulation.[9] Alternatively, forehead cooling might trigger peripheral release of noradrenaline from vasoconstrictor neurons which then excites a nociceptive focus in the CRPS-affected

limb.[23,24] However, if this was the only mechanism, cooling the contralateral forehead ought to have evoked limb pain as effectively as ipsilateral cooling.

Tingling sensations, muscle tightening, cramps or involuntary limb movements sometimes developed in the CRPS-affected limb when the ipsilateral forehead was cooled. Cramping pain and movement disorders in CRPS are not well understood, but might involve impaired integration of sensory input and motor output at multiple levels within the spinal cord and brain.[25] We previously reported that arousal stimuli evoked involuntary rhythmic movements of the legs and/or toes in two patients with features of CRPS.[26] In one patient, pain and toe movements disappeared after sympathetic blockade (implying aberrant peripheral interaction among sensory, motor and autonomic fibres) whereas, in the other patient, toe movements and allodynia to light tactile stimulation persisted during sympathetic blockade (implying aberrant central influences of arousal on pain and movement). Thus, it is tempting to speculate that motor symptoms in CRPS are mediated, at least in part, by aberrant interaction among sensory, motor and autonomic fibres in peripheral nerves and/or by noradrenergic arousal centres within the brainstem such as the locus coeruleus that send parallel projections to the dorsal and ventral horn.[27]

Loss of tactile discrimination in CRPS is associated with reorganization of the somatosensory cortex; this may be driven by nociception, as tactile discrimination improves and organization of the somatosenory cortex returns to normal when pain remits.[28-30] In the present study, sensitivity to light touch was diminished in the CRPS-affected limb of patients whose limb pain remained unchanged or decreased during ipsilateral forehead cooling. These findings suggest that tactile changes in the CRPS-affected limb (and, by implication, reorganization of the somatosensory cortex) were unrelated to disturbances in ipsilateral pain modulation.

We previously reported that signs of disturbance in ipsilateral pain modulation were detected more frequently in the later than early stages of CRPS, and that acoustic startle stimuli presented to the ipsilateral ear triggered greater increases in pain in the CRPS-affected limb than contralateral startle stimuli.[9] The mechanism of this ipsilateral nociceptive startle response is unknown, but is likely to be similar to the mechanism that underlies the nociceptive effect of ipsilateral forehead cooling (e.g., disrupted ipsilateral pain modulation). The association between the chronicity of CRPS and heightened nociceptive responses to ipsilateral startle and forehead cooling may reflect an evolution of symptoms from the early to the later stages of CRPS, or could indicate the presence of a distinct pathophysiological mechanism that develops early in CRPS but fails to resolve. Alternatively, hemilateral hyperalgesia might be a prognostic marker of vulnerability to persistent pain and/or CRPS. This will need to be explored prospectively in further studies.

Patients were asked not to take medication on the day of testing, but medication was otherwise maintained because it was considered unethical to risk triggering withdrawal symptoms. Although medication might have affected the intensity of symptoms, it seems unlikely that pharmaceutical agents would alter pain modulation on only one side of the body. Consistent with this, medication profiles were unrelated to the nociceptive effect of cooling the ipsilateral forehead.

Our findings necessarily are limited by the sample size and clinical characteristics of the patients studied. In most cases, CRPS began after a bone or soft-tissue injury without obvious peripheral nerve involvement, but in eight patients CRPS began after peripheral nerve injury (CRPS type II). Whether CRPS type I and II share similar mechanisms is uncertain; nevertheless, it is interesting to note that limb pain increased in a few patients with CRPS type II when the ipsilateral forehead was cooled but did not change during contralateral forehead cooling. In general, patients who reported that limb pain increased

during ipsilateral forehead cooling were more sensitive to pressure-pain in the limbs than the remainder of patients, and there was a similar trend for sharpness in the CRPS-affected limb. In addition, sensitivity to cold and heat was greater in the CRPS-affected than contralateral limb of patients who reported that limb pain increased during ipsilateral forehead cooling. A larger sample would be required to establish whether hyperalgesia to ipsilateral forehead cooling is associated with a particular pattern of symptoms in CRPS; however, our preliminary findings suggest that the intensity of symptoms in the CRPS-affected limb is important.

Heightened inflammation, autonomic dysfunction, central sensitization, disrupted endogenous pain modulation and additional neuroplastic changes within the central nervous system may all contribute to CRPS at various times in different patients.[1,31-34] In addition, we have identified a group of patients with a disturbance in sensory processing and pain modulation that involves the ipsilateral forehead. As CRPS is likely to be chronic in such cases, it is important to determine whether agents that alter activity ipsilaterally in pain modulation pathways help to alleviate pain and other symptoms in this subgroup of patients. For example, if aberrant activation of α_1-adrenoceptors within the central noradrenergic system contributes to hemilateral hyperalgesia in CRPS,[16-19] alpha-adrenergic antagonists such as prazosin may inhibit symptoms and pain.

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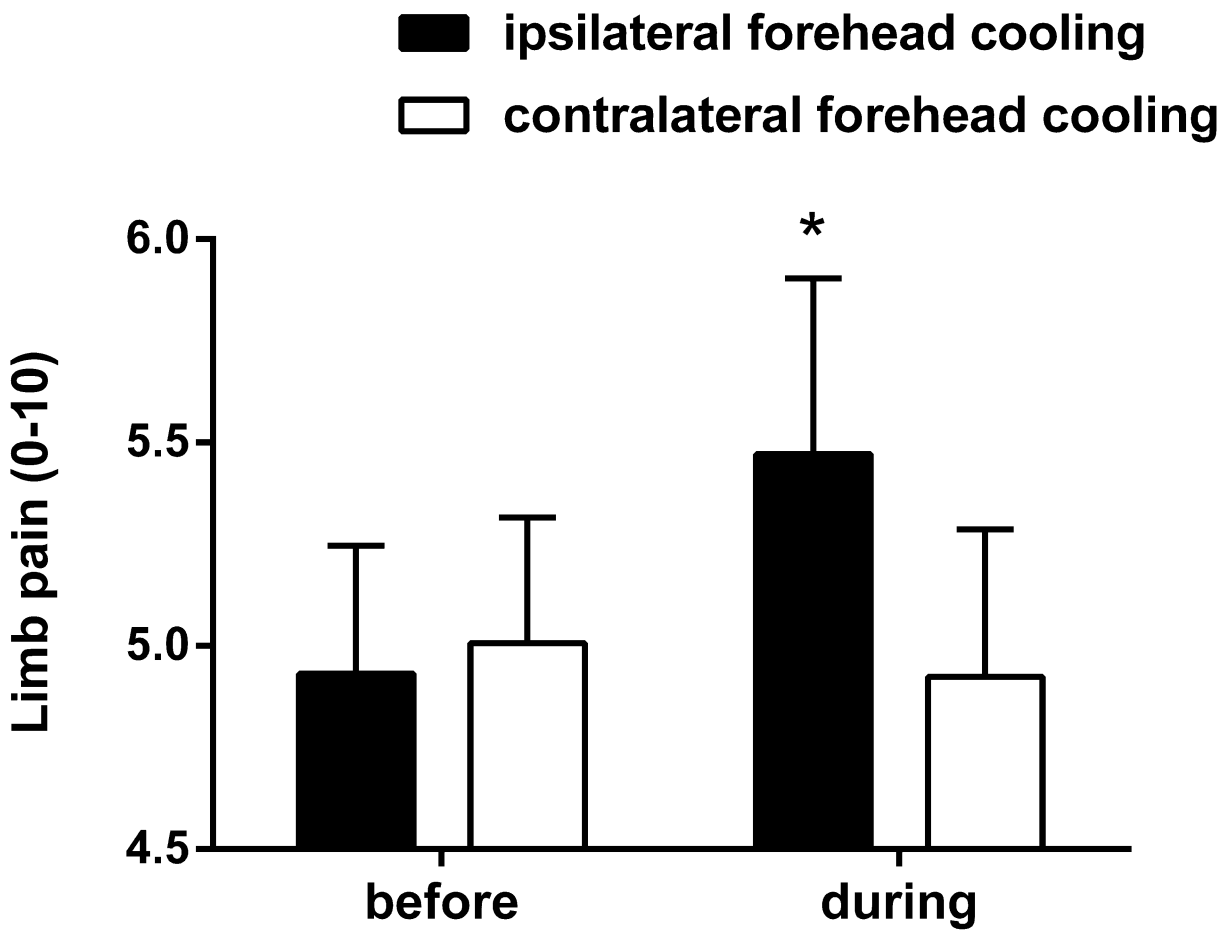
Figure legends

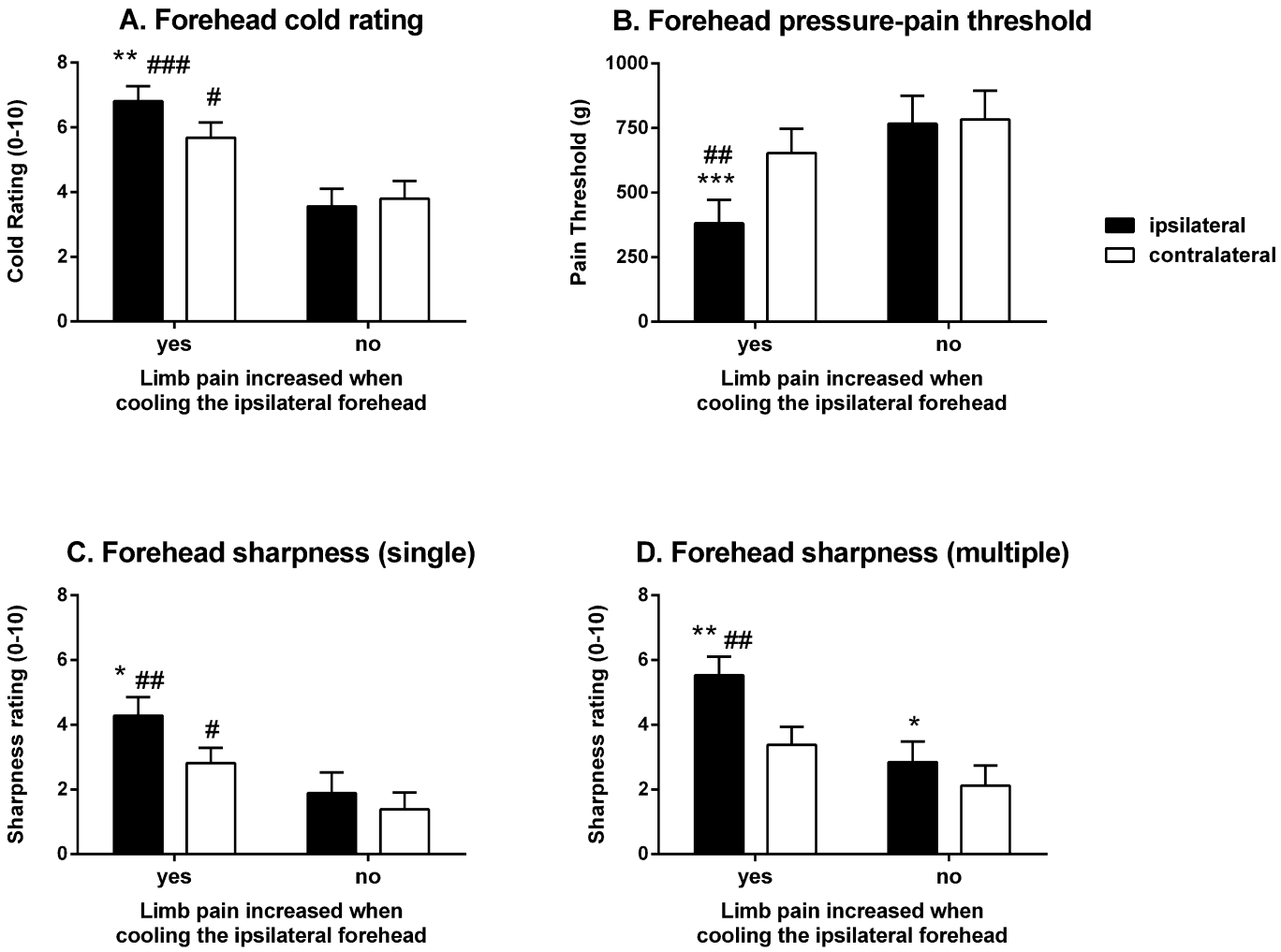
Figure 1. Pain ratings (± S.E.) in the CRPS-affected limb before and during ipsilateral and contralateral forehead cooling (2^{o}C) in 37 patients with CRPS (difference between the ipsilateral and contralateral side of the forehead statistically significant, * $p<0.05$).

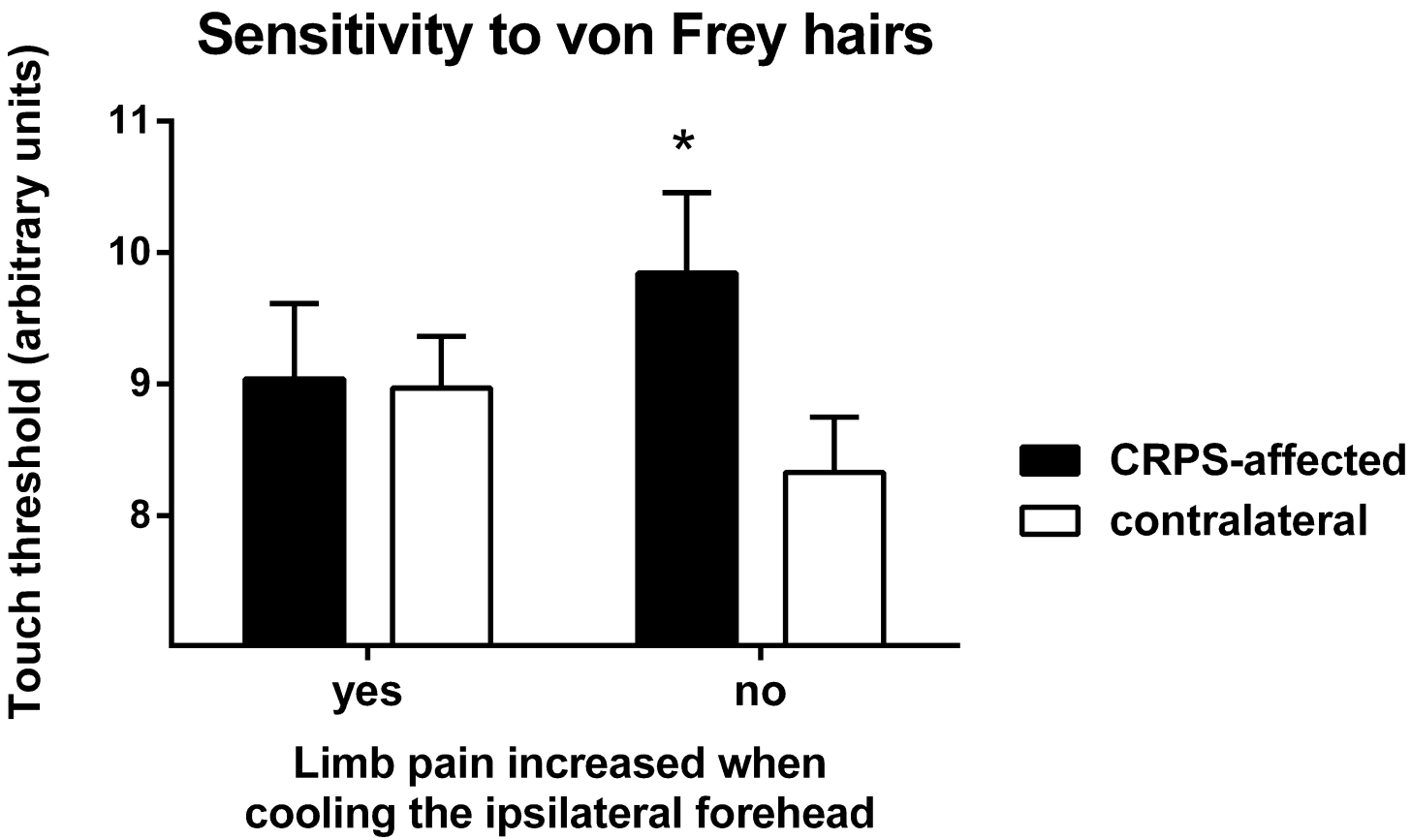
Figure 2. Cold ratings, pressure-pain thresholds and ratings of sharpness evoked by single and multiple applications of a von Frey hair (10 g bending force) on each side of the forehead in patients whose limb pain increased during ipsilateral forehead cooling (N = 16 to 21) or whose limb pain remained unchanged or decreased during ipsilateral forehead cooling (N = 13 to 16). The error bars represent standard errors. # indicates a significant difference between groups (# $p<0.05$; ## $p<0.01$, ### $p<0.001$), and * indicates a significant difference between the ipsilateral and contralateral sides of the forehead (* $p<0.05$; ** $p<0.01$; *** $p<0.001$).

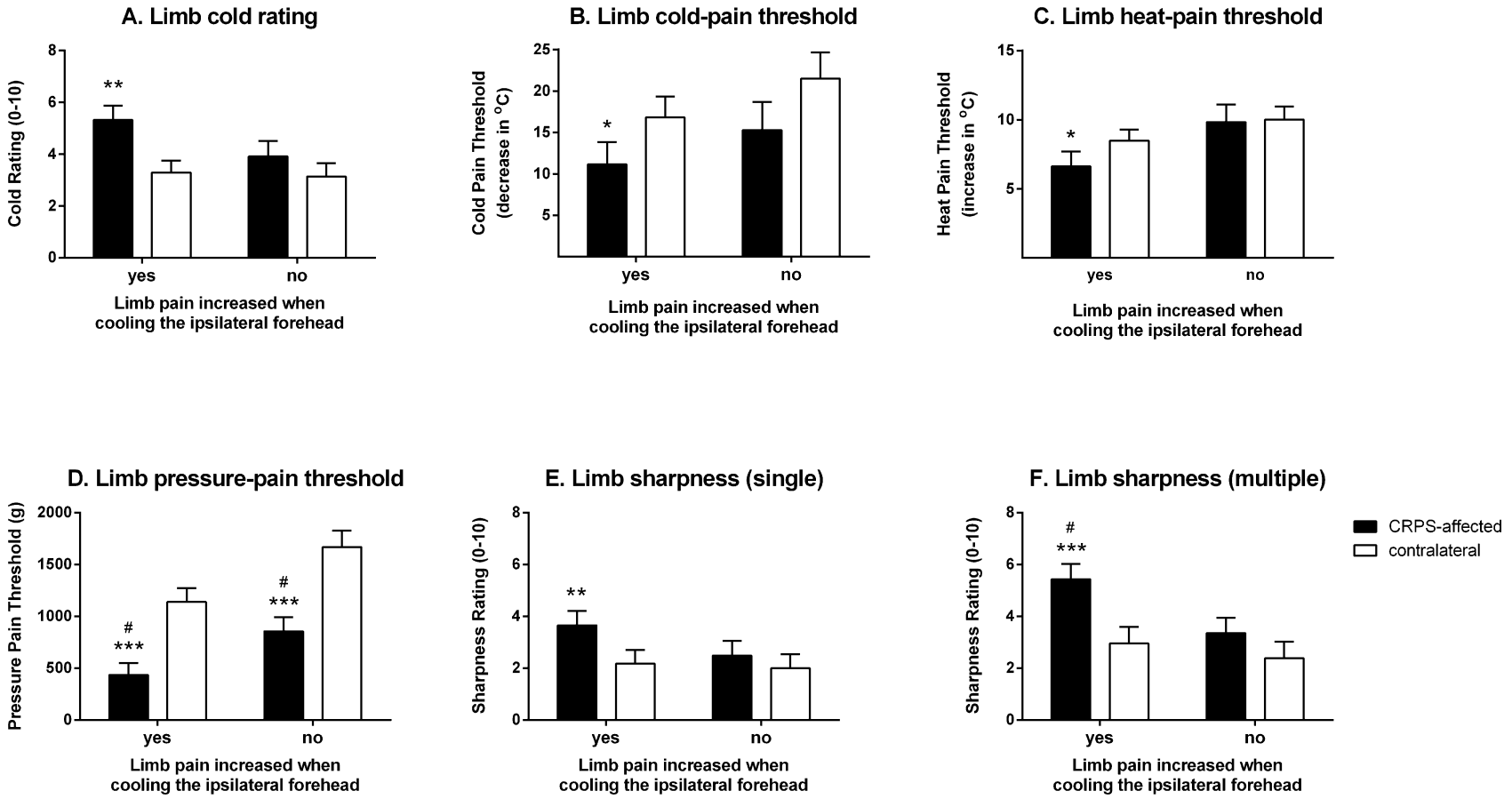
Figure 3. Sensitivity to light tactile stimulation with von Frey hairs in the CRPS-affected and contralateral limbs of patients whose limb pain increased during ipsilateral forehead cooling (N = 17) or whose limb pain remained unchanged or decreased during ipsilateral forehead cooling (N = 15). The error bars represent standard errors, and * indicates a significant difference between the CRPS-affected and contralateral limb ($p<0.05$).

Figure 4. Cold ratings, cold-pain thresholds, heat-pain thresholds, pressure-pain thresholds and ratings of sharpness evoked by single and multiple applications of a von Frey hair in the CRPS-affected and contralateral limbs of patients whose limb pain increased during ipsilateral forehead cooling (N = 15 to 21) or whose limb pain remained unchanged or decreased during ipsilateral forehead cooling (N = 11 to 15). The error bars represent standard errors. # indicates a significant difference between groups ($p<0.05$), and * indicates a significant difference between the CRPS-affected and contralateral limb (* $p<0.05$; ** $p<0.01$; *** $p<0.001$).


ipsilateral forehead cooling
contralateral forehead cooling
Limb pain (0-10)
6.0
5.5
5.0
4.5
*
before
during


A. Forehead cold rating
Cold Rating (0-10)
** ###
#
yes
no
Limb pain increased when cooling the ipsilateral forehead
B. Forehead pressure-pain threshold
Pain Threshold (g)
##
***
ipsilateral
contralateral
C. Forehead sharpness (single)
Sharpness rating (0-10)
* ##
#
D. Forehead sharpness (multiple)
** ##
*


Sensitivity to von Frey hairs
Touch threshold (arbitrary units)
11
10
9
8
*
yes
no
Limb pain increased when
cooling the ipsilateral forehead
CRPS-affected
contralateral


A. Limb cold rating
Cold Rating (0-10)
**
yes
no
Limb pain increased when cooling the ipsilateral forehead
B. Limb cold-pain threshold
Cold Pain Threshold (decrease in °C)
*
yes
no
Limb pain increased when cooling the ipsilateral forehead
C. Limb heat-pain threshold
Heat Pain Threshold (increase in °C)
*
yes
no
Limb pain increased when cooling the ipsilateral forehead
D. Limb pressure-pain threshold
Pressure Pain Threshold (g)
#
***
#
***
yes
no
Limb pain increased when cooling the ipsilateral forehead
E. Limb sharpness (single)
Sharpness Rating (0-10)
**
yes
no
Limb pain increased when cooling the ipsilateral forehead
F. Limb sharpness (multiple)
Sharpness Rating (0-10)
#
***
yes
no
Limb pain increased when cooling the ipsilateral forehead
CRPS-affected
contralateral