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# Optokinetic stimulation increases limb pain and forehead hyperalgesia in complex regional pain syndrome

**Running head:** CRPS: OKS increases limb pain and forehead hyperalgesia

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## What's already known about this topic?

- 1) Visual sensory conflicts induced by viewing ambiguous visual stimuli increase limb pain in complex regional pain syndrome
- 2) Motion sickness, a form of central neural sensory conflict (or sensory mismatch), can induce unpleasant sensations and scalp tenderness.
- 3) Optokinetic stimulation provides a mean to induce motion sickness

## What does this study add?

- 1) Limb pain and forehead hyperalgesia to pressure increased in CRPS patients in response to optokinetic stimulation
- 2) In the most nauseated subjects who withdrew early from optokinetic stimulation, the increase in hyperalgesia in the ipsilateral forehead persisted for a longer time.
- 3) The results suggest that sensory conflicts may increase limb pain in CRPS by activating mechanisms of general facilitation of nociception and, during more severe sensory conflicts, also a facilitatory mechanism which operates mainly ipsilateral to the affected limb.

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**Keywords:** complex regional pain syndrome; motion sickness; optokinetic stimulation; facilitation; sensory conflict

## **Abstract**

**Background:** Ambiguous visual stimuli increase limb pain in patients with complex regional pain syndrome (CRPS), possibly due to afferent sensory feedback conflicts. Conflicting sensory stimuli can also generate unpleasant sensations in healthy people such as during motion sickness. We wanted to investigate the mechanisms underlying the link between sensory conflicts and pain in CRPS using optokinetic stimulation – a method known to induce motion sickness.

**Methods:** 21 CRPS patients underwent optokinetic stimulation (OKS) and rated symptoms of motion sickness. Patients also rated limb pain and pain-related distress before, during and after OKS. In addition, pressure-pain and sharpness sensations were investigated on both sides of the forehead and in the affected and contralateral limb before and after OKS.

**Results:** Limb pain and forehead hyperalgesia to pressure increased in parallel in response to OKS. In a subgroup of nauseated patients who withdrew early from OKS, hyperalgesia to pressure in the ipsilateral forehead persisted longer than in the remaining participants. Sharpness sensations remained constant at all sites.

**Conclusions:** Sensory conflicts may facilitate pain in CRPS by activating mechanisms of general facilitation of nociception and, during more severe sensory conflicts, also a facilitatory mechanism which operates mainly ipsilateral to the affected limb.

## Introduction

Complex regional pain syndrome (CRPS) is a painful condition of the extremities characterized by an intense pain that outlasts the initial injury. The pain is accompanied by sensory disturbances, autonomic, motor and trophic changes. The symptoms may spread to other body sites (Maleki et al., 2000) and hyperalgesia, particularly to pressure, is often detected at sites outside the affected limb (Drummond and Finch, 2006; Knudsen et al., 2011; van Rooijen et al.).

Neuroplastic cortical changes probably contribute to CRPS. The cortical limb representation is reduced in primary and secondary somatosensory cortices (Juottonen et al., 2002; Maihofner et al., 2003; Pleger et al., 2004) and both increased and reduced cortical representation of the limb are found in the primary motor cortex (Krause et al., 2006; Maihofner et al., 2007). Furthermore, both the sensory (Juottonen et al., 2002; Maihofner et al., 2003; Vartiainen et al., 2008) and motor cortices are hyperexcitable (Eisenberg et al., 2005; Schwenkreis et al., 2003). Cortical reorganisation of sensory and motor systems, and the resulting incongruence between these systems, can lead to dysfunctional central integrative control and sensory feedback conflicts. This may contribute to signs and symptoms of CRPS, including self-perception disturbances and aggravation of pain (Cohen et al., 2012).

Visual-sensory conflict may increase pain and autonomic disturbances in CRPS. When viewing an ambiguous bi-stable image (the necker cube), 73% of patients reported heightened pain and sensory disturbances in the CRPS limb (Hall et al., 2011). In addition, patients reported feelings of disorientation and changes in temperature, weight, and perception of the affected limb (Hall et al., 2011). 13% of the patients had such a severe worsening of their symptoms that the task was discontinued. In a similar study which also investigated autonomic responses using laser doppler flowmetry, pain increased in 61% of patients while viewing ambiguous visual stimuli, and an asymmetric mixed vasomotor response developed in about half of these (Cohen et al., 2012). In ten patients, dystonic reactions were associated with increases in pain. 50% of these also experienced an asymmetric vasomotor response to viewing, consistent with incongruence between sensory, motor and autonomic systems when viewing ambiguous visual stimuli.

Sensory conflicts can also generate unpleasant sensations such as motion sickness. The almost universally accepted explanation of motion sickness is that it arises, at least partially, from a central neural sensory conflict or mismatch between sensory inputs about body position (e.g., from the eyes, the vestibular system and nonvestibular proprioceptors) (Warwick-Evans et al., 1998). Interestingly, motion sickness (nausea) following optokinetic stimulation was associated with an increase in scalp

tenderness in the forehead of migraineurs and healthy controls (Drummond, 2002). Thus, we hypothesized that a sensory conflict that evoked symptoms of motion sickness would enhance pain and sensory disturbances in the CRPS limb and elsewhere. In particular, as CRPS is often associated with pressure hyperalgesia in the forehead ipsilateral to the symptomatic limb, we hypothesized that this hyperalgesia would intensify during motion sickness.

## **Methods**

### *Participants*

Twenty-one participants with CRPS (6 males, 15 females, mean age  $40.48 \pm 2.87$ ) who were seen at a small private pain medicine centre were studied. The International Association for the Study of Pain diagnostic research criteria for CRPS (Harden et al., 2007) were fulfilled by all patients. The upper limb was affected in 10 patients (7 right, 3 left) and the lower limb in 11 patients (7 right, 4 left). Pain had developed after a fracture (9 patients), soft tissue injury or sprain (4 patients), surgery or infection (4 patients), clotting, electric shock or anaphylactic reaction (3 patients), and nerve lesion (1 patient). 19 patients were considered to have CRPS I and 2 patients CRPS II. Pain had persisted from 2 months to 19.2 years (median duration 4.5 years). Most patients were receiving treatment with analgesics, anticonvulsants or antidepressants but 6 patients did not take regular medication. For ethical and practical reasons, patients were not asked to abstain from medication during the study. 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. The study was approved by the Murdoch University Human Research Ethics Committee and written informed consent was obtained from each participant. The study conformed with the Helsinki Declaration of 1975, as revised in 1983.

### *Procedures*

*Pain and sensory disturbances in the CRPS limb:* Patients rated pain in their affected limb on a scale from 0 (no pain) to 10 (extremely severe pain), and they also rated the distress associated with pain on a similar scale (0, no distress, 10 extremely severe distress). A spring loaded algometer with a rounded tip (1 cm in diameter) was used to assess pressure-pain thresholds (PPT) in the affected and contralateral limbs. Pressure was applied in 200 g increments to a maximum of 2.3 kg or until pain was reported (Finch et al., 2009). 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). Enough force was applied to bend the bristle for 1 s (Finch et al., 2009).

*Forehead sensitivity:* Pressure was applied on each side of the forehead at intervals of 80 g until the participant reported pain (Finch et al., 2009). In addition, sharpness was assessed using the procedure outlined above.

*Optokinetic stimulation (OKS):* Patients were seated on a stationary chair. To induce symptoms of motion sickness, patients placed their head and shoulders inside a drum (50 cm in diameter, 70 cm in height) which was painted internally with 24 pairs of 3.3 cm wide vertical black and white stripes and well-lit (Drummond, 2002). The drum revolved 10 times per minute for 10 min or until participants could no longer tolerate the sensations evoked by OKS. To enhance the illusion of movement, patients were asked to look at a distant point rather than watch the stripes move past. The conflict between the visual illusion of movement and contrasting vestibular and proprioceptive cues from actually sitting still may induce motion sickness. Symptoms of motion sickness (dizziness, nausea and headache) were rated by the patients from 0 (none) to 10 (extremely severe). Participants were also asked whether they experienced an illusion of movement (yes, no).

*Trial sequence:* Sessions took place in a laboratory maintained at  $20 \pm 2$  °C. Sensitivity to mechanical stimulation on each side of the forehead and in each limb was assessed before OKS as was motion sickness symptoms and ratings of pain and distress associated with pain in the CRPS limb. The participants then underwent OKS. Every 2 min during OKS and straight after OKS, the participants reported the pain and distress associated with the CRPS limb along with motion sickness symptoms and whether they experienced an illusion of movement. Immediately after OKS, forehead and limb sensitivity assessments were repeated at two-minute intervals for 12 minutes.

#### *Statistical approach*

To investigate changes in pain in the CRPS limb, pain-related distress and symptoms of motion sickness (dizziness, nausea and headache) during and after OKS, levels at each time point were compared with levels at baseline using paired t-tests. This planned approach was used as seven of the 21 patients withdrew before the full ten minutes of OKS. Next, symptoms after OKS were compared between patients who lasted the full ten minutes and those who withdrew early in Group x Time (before versus each time point after OKS) analyses of variance. The Greenhouse-Geisser epsilon was used to correct for violations of the sphericity assumption. Significant interactions between levels at baseline and levels at each time point after OKS were investigated using a step-down approach with

t-tests. Changes in hyperalgesia to pressure-pain and sharpness after OKS had an additional factor of Side (ipsilateral versus contralateral to the symptomatic limb). Finally, the association between changes in limb pain and changes in hyperalgesia and symptoms of motion sickness immediately after OKS was explored using Pearson's correlation coefficient. No correction for multiple tests was made as these correlations were exploratory. The criterion of statistical significance was  $p < 0.05$ .

## Results

### *Symptoms of motion sickness and limb pain*

Within 2 minutes of OKS, all but one patient reported that the rapidly-revolving stripes inside the optokinetic drum appeared to slow down or stop and, at the same time, to take on a 3-dimensional aspect and to appear wider and more distant than before the drum started to revolve. This was often associated with a sense that the stationary chair was spinning. The other participant reported a visual illusion of movement 4 minutes into the rotation. Dizziness and nausea increased progressively during OKS, and gradually subsided after the drum stopped revolving (Fig. 1). Headache developed more slowly, but persisted during the entire 12-minute follow-up period. Importantly, pain in the CRPS limb increased significantly after four minutes of OKS, and this increase persisted for several minutes afterwards (Fig. 1). However, the distress associated with limb pain did not change either before or after OKS.

➤ Please insert Fig. 1 here.

Seven patients withdrew early from OKS – two within 2 minutes, two after 4-5 minutes, another two after 6-7 minutes, and one after 8.5 minutes. Immediately after OKS, nausea was greater in this group than in patients who remained in the optokinetic drum for the full 10 minutes [main effect for Group,  $F(1,19) = 4.43$ ,  $p < 0.05$ ; Group x Time interaction,  $F(2.25, 42.71) = 4.18$ ,  $p < 0.05$ ] (Fig. 2). However, dizziness, headache and limb pain ratings were similar in both groups both before and after OKS.

➤ Please insert Fig. 2 here.

### *The effect of motion sickness on hyperalgesia in the CRPS limb and forehead*

After OKS, the PPT decreased on both sides of the forehead, and this heightened sensitivity persisted for the entire 12-minute follow-up period [main effect for Time,  $F(4.14, 82.76) = 7.31$ ,  $p < 0.001$ ]

(Fig. 3). However, the PPT and sharpness ratings remained stable in the CRPS limb, as did sharpness ratings for the forehead (Fig. 3).

➤ Please insert Fig. 3 here.

In patients who withdrew early from OKS, hyperalgesia to pressure persisted longer during the recovery period on the ipsilateral than contralateral side of the forehead [Group x Time x Side interaction,  $F(4.00, 75.94) = 4.13, p < 0.01$ ] (Fig. 4). However, hyperalgesia subsided at a similar rate on both sides of the forehead in patients who tolerated the full 10 minutes of OKS.

➤ Please insert Fig. 4 here.

Increases in pain in the CRPS limb during OKS were associated with decreases in the PPT in the forehead when measured immediately afterwards [ $r(19) = -0.51, p < 0.05$ ] (Fig. 5). This association appeared to be specific, as increases in limb pain were unrelated to other indices of hyperalgesia (changes in pain-related distress or in sensitivity to pressure or sharpness in the CRPS limb, or changes in sharpness in the forehead) or to indices of motion sickness (duration of OKS, or increases in dizziness, nausea or headache).

➤ Please insert Fig. 5 here.

### **Discussion and conclusions**

The main finding of the present study was that limb pain increased in response to OKS and that this seemed to be linked with the visual illusion itself (i.e., the sensory conflict) rather than motion sickness. In particular, both the visual illusion and dizziness began before limb pain increased, but dizziness was unrelated to the increase in limb pain. Furthermore, although nausea increased at the same time as limb pain, nausea was unrelated to the increase in pain. In addition, headache did not develop until after the limb pain had developed, making headache an unlikely contributor to the increase in pain. This is consistent with findings that ambiguous visual stimuli increase CRPS pain. Cohen and colleagues (Cohen et al., 2012) speculated that cortical reorganization in sensory (Juottonen et al., 2002; Maihofner et al., 2003; Pleger et al., 2004) and motor cortices (Krause et al., 2006; Maihofner et al., 2007) may contribute to this by causing incongruence between sensory and motor systems and thus problems with the integration of afferent sensory input. Consistent with this, they found asymmetric vasomotor responses and dystonic reactions in the affected limb of patients whose pain increased when viewing ambiguous visual stimuli (Cohen et al., 2012).



The present findings suggest an additional mechanism by which sensory conflicts may increase pain in CRPS. Sensitivity to pressure increased on both sides of the forehead when measured immediately after OKS, and the sensitivity persisted for the remainder of the assessments. This increase was associated with an increase in limb pain, suggesting a shared mechanism such as the recruitment of generalized facilitation of nociception during exposure to sensory conflicts or disruption of inhibitory controls. Top-down pain modulation (inhibition *and* facilitation) emanates from brain sites such as the serotonergic raphe nuclei (Millan, 2002; Zhuo and Gebhart, 1997). A bilateral increase in forehead sensitivity to pressure was also found during noxious cold water immersion of the affected or unaffected limb in patients with CRPS (Knudsen et al., 2011), suggesting that generalized facilitation is easily recruited in this patient group.

Interestingly, in the patients who withdrew early from OKS, the hyperalgesic effect of OKS on ipsilateral forehead hyperalgesia persisted longer than in the group who stayed in the drum for the entire period. These patients reported greater intensity of nausea, suggesting that they experienced a greater degree of sensory conflict. Thus, there appears to be a link between increased sensory conflict and the persistence of ipsilateral forehead hyperalgesia. The mechanism of this is unknown, but might involve supraspinal sites such as the thalamus contralateral to the affected limb which has multi-systemic connections (e.g., visual, auditory, motor, sensory) (Budinger et al., 2006; Cappe et al., 2009; Cappe et al., 2012; Komura et al., 2005), and thus may be influenced by afferent sensory feedback conflicts. Cortical reorganization in CRPS (Juottonen et al., 2002; Maihofner et al., 2003; Pleger et al., 2004) may provide an additional explanation. Shrinking of the cortical area representing the affected limb in the somatosensory cortex may explain increased pain signaling during OKS not only in the cortical limb area but also in nearby cortical areas such as the ipsilateral forehead. If so, we would expect the persistence of forehead hyperalgesia to be greater in upper limb CRPS patients than lower limb patients due to the near proximity of cortical hand and head representations. Unfortunately, the early withdrawal group was too small to conduct statistical analysis of this, but 4/7 patients (57%) in the early withdrawal group experienced pain in an upper limb compared to 6/21 (29%) in the remaining group, providing some support for this. However, headache did not arise until much later. Unfortunately, we did not document the location of patients' headache which, in the case of cortical reorganization, would be expected to be greater ipsilaterally.

The findings may also suggest the recruitment of a mechanism which facilitates nociception by operating predominantly on the side of the body ipsilateral to the affected limb in the most nauseated subjects. In a previous study, greater increases in forehead hyperalgesia in the ipsilateral than the contralateral forehead of CRPS patients were likewise found in response to painful cold water

immersion of the affected limb (Knudsen et al., 2011), consistent with the possibility of a mechanism that facilitates pain mainly on the ipsilateral side of the body. An increase in limb pain does not seem to initiate this mechanism as increases were similar in patients who withdrew early from the drum and those who remained in the drum for the entire period.

The mechanism of hemilateral facilitation is unknown. The locus coeruleus is involved in hemilateral antinociception on the side ipsilateral to the inflamed hindpaw during carrageenan-induced hindpaw inflammation (Tsuruoka et al., 1999; Tsuruoka et al., 2004; Tsuruoka et al., 2003), but may also facilitate pain by stimulating excitatory  $\alpha_1$ -adrenoceptors in spinal nociceptive pathways (Hedo and Lopez-Garcia, 2001). Perhaps, in some CRPS patients, impairments in inhibitory projections from the LC unmask hemilateral facilitation. This mechanism may have been activated in the most nauseated patients in the present study. Perhaps the sensory conflict experienced by the other group was not severe enough to activate this mechanism. Alternatively, the presence of ipsilateral forehead hyperalgesia in the patients who withdrew early from the drum versus the bilateral forehead hyperalgesia in those who remained in the drum for the entire period simply reflects variability in the duration of sensory conflict. During sensory conflict, hyperalgesia may initially present itself ipsilaterally and then become bilateral with longer sensory conflict duration, reflecting the spread of sensitization or facilitation of nociception in the central nervous system.

Curiously, despite an increase in limb pain and forehead hyperalgesia to pressure, hyperalgesia did not change in the affected limb in response to OKS. This suggests that different mechanisms contribute to spontaneous limb pain and hyperalgesia to pressure and sharpness in the CRPS limb. Patients with CRPS often describe their spontaneous pain as a deep burning sensation (Birklein et al., 2000; Rommel et al., 1999). Spontaneous limb pain may thus be located in deeper structures such as bones rather than skin (sharpness) or muscle (pressure). Bone marrow, mineralized bone and the periosteum are highly innervated by nerve fibers (Calvo and Forteza-Vila, 1969; Hara-Irie et al., 1996; Mach et al., 2002; Thurston, 1982). An increasing number of studies suggest that different mechanisms underlie sensibility in skin versus muscle both in healthy humans and chronic pain populations such as CRPS and fibromyalgia (Henderson et al., 2006; Knudsen and Drummond, 2009; Mailis and Bennett, 2002; Mense, 2003). That forehead sensitivity to pressure, but not sharpness, changed in response to OKS in the present study provides further evidence of this. For obvious reasons, pain and sensibility in deeper somatic structures such as bone and fascia is a largely neglected area in pain research but should be investigated further.

Why pressure hyperalgesia increased in the forehead, but not in the CRPS limb, is unclear. Perhaps the smaller intervals in pressure-pain assessments in the forehead made the assessments more sensitive at detecting changes than in the limb. Alternatively, trigeminal second-order nociceptive neurons may be more easily sensitized to sensory conflicts than nociceptive neurons elsewhere. This would be consistent with the well-known occurrence of headache but not body ache during motion sickness. In support of this, scalp tenderness developed in nauseated healthy controls and migraineurs during OKS, but not in the fingertips of healthy controls (Drummond, 2002).

A potential limitation of this study is that the sample consisted of a small number of mainly chronic treatment-resistant CRPS patients who may differ from acute CRPS patients. In addition, patients remained on their regular medication. However, medication would be expected to suppress, not increase, pain and hyperalgesia. Another limitation is that the study relied on self-report measures which may be subject to bias. However, this is unlikely to have played a major role as the patients were unaware of the aim of the study. Future studies should adopt more objective measures of physiological functioning in addition to self-report ratings, and investigate CRPS responses to other means of motion sickness induction as only some of the patients reported symptoms of motion sickness during OKS.

In conclusion, the present findings suggest that sensory conflicts activate mechanisms of general pain facilitation in CRPS and, in the most nauseated subjects, also activate a pain facilitatory mechanism which operates mainly ipsilateral to the affected limb. Thus, conflicting sensory information in CRPS such as that about the position of the affected limb in space (Moseley et al., 2013) could be a source of pain.

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### **Author contributions**

Both authors contributed to the design of the study and the writing and intellectual content of the manuscript. LK was responsible for data collection, and PDD for the statistical analysis. Both authors discussed the results and approved the final version of the article.

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## Figure legends

Figure 1. Changes ( $\pm$  S.E.) in (a) pain in the CRPS limb, (b) pain-related distress and (c-e) symptoms of motion sickness (dizziness, nausea and headache) during and after optokinetic stimulation. As seven of the 21 patients withdrew before the full ten minutes of optokinetic stimulation, each data point during and after stimulation was compared with levels at baseline using paired t-tests (\*  $p < 0.05$ ).

Figure 2. Changes ( $\pm$  S.E.) in nausea after optokinetic stimulation in 14 patients who tolerated the full ten minutes of optokinetic stimulation and seven patients who withdrew early. Nausea was greater for several minutes after optokinetic stimulation in patients who withdrew early (# independent samples t-tests,  $p < 0.05$ ).

Figure 3. Changes ( $\pm$  S.E.) in the (a) PPT and (b) sharpness ratings in the CRPS and contralateral limb, and in the (c) PPT and (d) sharpness ratings on each side of the forehead, after optokinetic stimulation. The PPT decreased on both sides of the forehead after optokinetic stimulation (# mean PPT significantly lower than baseline,  $p < 0.05$ ).

Figure 4. Changes ( $\pm$  S.E.) in the PPT on each side of the forehead after optokinetic stimulation in the (a) 14 patients who tolerated the full ten minutes of optokinetic stimulation and the (b) seven patients who withdrew early. The PPT recovered more slowly after optokinetic stimulation on the ipsilateral than contralateral side of the forehead in patients who withdrew early (# planned Group x Side contrasts between baseline and each data point after optokinetic stimulation,  $p < 0.05$ ).

Figure 5. Association between increases in pain in the CRPS limb during optokinetic stimulation and decreases in PPT in the forehead straight afterwards.