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The effect of tactile discrimination training is enhanced when patients watch the reflected image of their unaffected limb during training

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ABSTRACT

In patients with phantom limb pain or complex regional pain syndrome (CRPS), sensory discrimination training increases tactile acuity, normalises cortical reorganisation and decreases pain. In healthy people, sensory cortical response, and tactile acuity, are greater if the participant looks towards the body part being stimulated. Does this effect enhance tactile training in CRPS patients? Ten patients underwent a 30-min tactile discrimination training session under four conditions (order randomised) in a 2×2 design: looking towards or away from the stimulated limb and seeing or not seeing skin. Tactile training imparted long-term improvement in tactile acuity when patients watched the reflected image of their unaffected limb in a mirror during training (that is, they looked towards the stimulated body part and could see the skin of the opposite body part in the mirror): two-point discrimination threshold (TPD) was 8 mm less 2 days after training than it was before training ([95% CI = 1.5–14.3 mm], $p < 0.001$). Although this condition also imparted a greater reduction in resting pain at post-treatment than the other conditions, and change in pain and change in TPD over the session were strongly related ($r = 0.83$, $p < 0.001$), there was no residual effect on pain at 2-day follow-up. In the other conditions, tactile acuity had returned to pre-training levels at 2-day follow-up. The results should directly improve management of CRPS, and have implications for rehabilitation of other conditions associated with nervous system injury or disease, for example stroke, in which tactile recovery is a major objective of rehabilitation.

1. Introduction

Tactile dysfunction is common after nervous system injury, for example stroke [3], multiple sclerosis [22] and complex regional pain syndrome (CRPS) [1]. In CRPS, and phantom limb pain, decreased tactile acuity relates to reorganisation of primary sensory cortex and to pain [5,12]. In phantom limb pain, sensory discrimination training reduces pain, increases sensory acuity and normalises cortical reorganisation [4]. In CRPS, tactile training increases tactile acuity and reduces pain [17] and recovery is also associated with normalisation of cortical reorganisation [13]. Now that a positive effect of sensory training has been demonstrated, it would seem prudent to pursue mechanisms to increase this effect.

In healthy volunteers, looking towards the stimulated body part enhances sensory processing. For example, looking towards a tactile stimulus increases primary somatosensory cortex (S1) response to touch [11] and seeing the skin of the body part being stimulated decreases the threshold for two-point discrimination (TPD). TPD is further decreased if the visual input of the skin is magnified [9]. In fact, improvement in tactile performance is still measurable after the visual input has been removed [23,27], which suggests that visual input may not only modulate synaptic drive, but also induce long-term changes. This raises the possibility that visual input of skin, and looking towards the body part, may improve the effect of tactile training in people with CRPS.

So far, the effect of multisensory integration on tactile function in people with sensory impairment, has only investigated real-time tactile performance: TPD threshold was less when post-stroke patients could see the stimulated limb than when they could not [24]. We investigated whether looking towards, and seeing the skin of, the stimulated part can impart a sustained increase in tactile acuity in patients with CRPS. We hypothesised that a single 30-min tactile discrimination session would impart a greater increase in tactile acuity if, during the training, participants looked towards the stimulated area and could see skin, than if they could not.

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2. Methods

2.1. Participants

Ten patients with chronic CRPS of one hand or wrist (diagnosed according to Bruehl et al. [2]) were recruited from physiotherapy and general practice clinics (Table 1). Informed consent was obtained and all procedures were in accordance with the Helsinki Declaration and were approved by the Institutional Ethics Committees.

2.2. Tactile discrimination training

All jewelleries were removed from both hands. Tactile discrimination training has been described in detail elsewhere [17]. On a digital photograph of the affected limb, five points were marked (Fig. 1A). All five points were located in the affected area. The distance between points was approximately the same as the TPD established for that area in that participant. Pilot data suggested that this rule provides a success rate of about 80% when participants attempt to identify which point was stimulated (see discrimination condition below). Two cork probes (2 mm and 11 mm in diameter, respectively) were mounted atop a spring-loaded cartridge such that the pressure with which each probe could be applied to the skin was standardised. Pressure was kept to a minimum to avoid provocation of pain. A screen was positioned to prevent the subject from seeing the affected area. Stimulation involved applying one of the probes to one of the marked points. The type of probe and the marked point were randomised using a random numbers table. Interstimulus interval was 15 s. Three 6-min blocks of 24 stimuli were undertaken with a 3-min rest period between blocks. Thus, each treatment session involved 72 stimuli and lasted for 24 min.

2.3. Experimental conditions

Training was performed under four different conditions, undertaken in separate sessions. The conditions were: (1) Facing + Skin: Participants watched a reflected image of the opposite (unaffected) arm, in a mirror that was placed between the limbs. The limbs were positioned in such a way that the reflected image of the opposite arm was in line with the stimulated arm (Fig. 1B). This permitted the participants to look towards the stimulated arm and to receive visual input of skin. In fact, this condition involved visual appreciation of the entire hand, not just visual input of skin. That is, participants could see a hand the position of which was congruent with the felt position of the hand that is being stimulated, a hand they felt to be theirs, not simply the skin of someone else's hand. (2) Skin only: Participants looked at the skin of the opposite arm (Fig. 1C). This permitted visual input of skin but did not permit

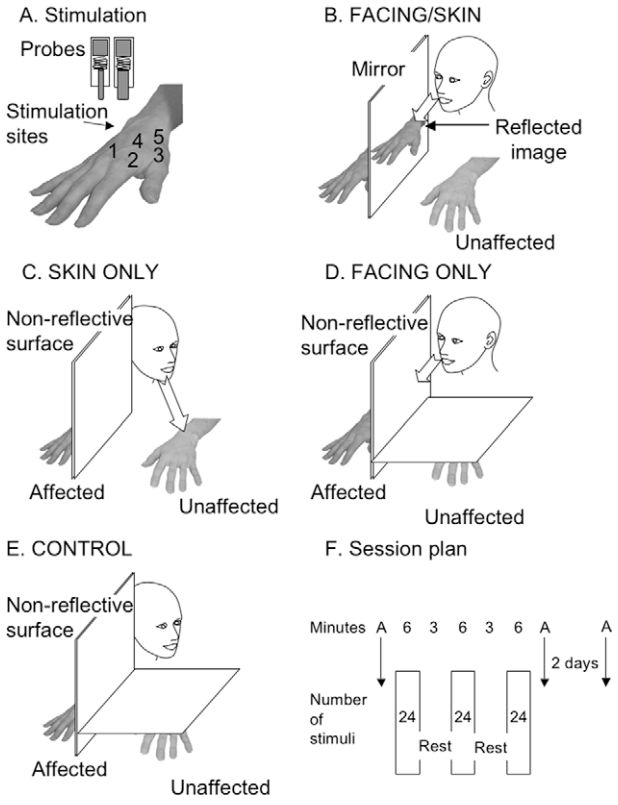

Fig. 1. Experimental protocol. (A) Two probes (2 mm and 12 mm in diameter) were applied to one of five stimulation sites on the affected limb (numbered) in a random order. (B) The Facing + Skin condition involved watching the reflected image of the non-stimulated arm while facing the stimulated arm. (C) The Skin only condition involved watching the non-stimulated arm directly. (D) The Facing only condition involved looking in the direction of the stimulated arm but with no mirror and the unaffected limb hidden. (E) The Control condition involved looking away from the stimulated limb with the unaffected limb hidden. (F) Each session involved 3 × 6 min blocks of 24 stimuli. Two-point discrimination and resting pain were assessed (denoted by 'A' and downward arrow) before, after and 2 days after training.

Table 1
Subject characteristics. Mean (M) and standard deviation (SD) are shown in bold italics. S, sex – M, male; F, female, age in years; L/R, affected limb – L, left; R, right; Part, body part injured; MOI, mechanism of injury; For Part/MOI: #, fracture; Sp, sprain; Dis, dislocation; CTS, carpal tunnel syndrome; Dur, duration in months since injury; asterisk denotes signs or symptoms present at initial assessment: H, hyperalgesia; A, allodynia; T, temperature changes; C, colour changes; E, edema; S, sudomotor changes; M, motor changes; and Tr, trophic changes. VAS, visual analogue scale for average pain intensity over previous 2 days; Fn, function as measured by task-specific numerical rating scale; medications as reported at initial assessment.

S (Age)	L/R	Part/MOI	Dur	Symptoms								Signs									Medications
				H	A	T	C	E	S	M	Tr	H	A	T	C	E	S	M	Tr	VAS	Fn	Prescribed (unprescribed)
M (62)	L	Hand cannula	19	*	*					*		*	*	*		*	*	*		5	3	Tramadol, paracetamol, codeine, and vitamin C
F (36)	L	Hand #	30	*	*	*		*			*	*	*	*		*	*		*	5	0	Gabapentin, amytryptiline (paracetamol)
F (58)	L	Wrist #	22	*	*			*				*	*	*					*	9	1	Amytryptiline
M (42)	L	Hand Sp	19	*	*		*				*	*	*		*				*	5	3	Morphine, amytryptiline, and tramadol (aspirin)
M (46)	R	Thumb Dis	19	*	*	*			*			*	*		*	*			*	9	0	Nil reported
M (53)	R	Hand Sp	12	*	*	*	*		*			*	*							6	2	Morphine, tramadol
F (32)	L	Wrist #	22	*	*						*	*	*	*					*	9	1	Naprogesic
F (33)	R	CTS	23	*	*	*	*		*			*	*		*	*				6	1	Morphine (cannabis, paracetamol)
F (41)	L	CTS	23	*	*		*				*	*	*	*		*			*	6	1	Amytryptiline, tramadol
F (28)	R	Wrist #	15	*	*	*	*				*	*	*				*		*	6	0	Nil reported
***M* = 43**			**20**																	7	1	
***SD* = 11**			***5***																	*2*	*1*	

looking towards the stimulated arm. (3) Facing only: Participants looked in the direction of the stimulated arm, although that arm was hidden from view (Fig. 1D). This permitted looking in the direction of the stimulated arm but did not permit receiving visual input of skin. (4) Control: Participants looked in the direction of the opposite arm, which was hidden from view (Fig. 1E). This permitted neither looking towards the stimulated arm, nor seeing visual input of skin. The Control condition was most similar to the approach for which there is evidence of a cumulative effect of daily training sessions [17].

There were 16 sessions for each participant. The conditions were randomised and counterbalanced so that each participant had four sessions of each condition, but in varying order. Each session involved three 6-min blocks of 24 stimuli for which both stimulus site and probe type were randomised. The interval between stimuli was 15 s. Blocks were separated by 3 min of rest (Fig. 1F). There were 3–4 days sessions inbetween. That is, there were 1–2 days between the follow-up assessment and the next training session. Participants were advised not to undertake tactile training inbetween sessions.

2.4. Assessments

2.4.1. Change in two-point discrimination threshold (TPD)

TPD was tested at three sites on the affected limb with a mechanical caliper (precision = 1 mm, applied until the very first blanching of the skin). A photograph recorded the location of TPD testing for each participant, so as to standardise that across sessions. To ensure that the results reflected cutaneous sensibility, the pressure was kept to a minimum. Testing commenced with 0 mm between the points of the calliper. The distance was gradually increased in 1 mm steps until the subject perceived two points instead of one. Once the participant reported perceiving two points instead of one, the following responses confirmed the determined threshold: (i) the subject reported a single point when the distance between calliper points was decreased below threshold, (ii) the subject reported two points when the distance between calliper points was increased back to the determined threshold, and (iii) the subject reported a single point when a single point was applied. The TPD for the three sites was averaged to provide a measure at pre-training, post-training and 2 days later. TPD was the primary outcome variable.

2.4.2. Change in resting pain

Participants were asked to rate their current pain using a 100 mm visual analogue scale (VAS), anchored at left with "no pain" and at right with "worst possible pain". Participants responded to the question "What level of pain do you have right now?" This measure, called pain, was the secondary outcome variable. Participants were advised to report any instantaneous pain caused by testing TPD or by training.

2.5. Statistical analysis

We used a within-subject model to test the experimental hypothesis.

To test the primary hypothesis that a single 30-min tactile discrimination session would impart a greater increase in tactile acuity if, during the training, participants looked towards the stimulated area and could see the skin, than if they could not, we undertook 3×4 factorial repeated measures ANOVA with the factors Time (three levels: pre-session, post-session and 2-day follow-up) and Condition (four levels: Facing + skin, Skin only, Facing only, and Control) on TPD. We replicated this ANOVA on our secondary outcome variable, resting pain. Significance was set at $p < 0.05$.

To test whether the change in TPD related to the change in Pain, we pooled data across conditions and undertook a linear regression, with significance set at $p < 0.05$. The data analysis was performed with SPSS Version 16 (SPSS, Inc., Chicago, Illinois, USA).

3. Results

3.1. Primary outcome variable: two-point discrimination threshold (TPD)

Tactile acuity, as measured by TPD, was improved with training, regardless of condition (main effect of Time ($F(2, 78) = 21.73$, $p < 0.001$). There was a main effect of condition on TPD ($F(3, 117) = 7.49$, $p = 0.009$), but this was driven by differences in TPD between conditions at post-session and at 2-day follow-up (Time $\times$ Condition interaction ($F(6, 234) = 11.34$, $p = 0.002$).

3.1.1. Short-term effect

Post-hoc testing revealed that TPD decreased more in the Facing + Skin condition, than it did in the other three conditions ($p < 0.025$ for all, Fig. 2). TPD decreased more in the Facing Only and the Skin Only condition than it did in the Control condition ($p < 0.05$ for both), but there was no difference between Facing Only and Skin Only (Fig. 2).

3.1.2. Sustained effect (2-day follow-up, testing the primary hypothesis)

Post-hoc testing revealed that the decrease in TPD between pre-session and 2-day follow-up was greater in the Facing + Skin condition, than it was in the other three conditions ($p < 0.025$ for all, Fig. 3), but there was no difference between those conditions

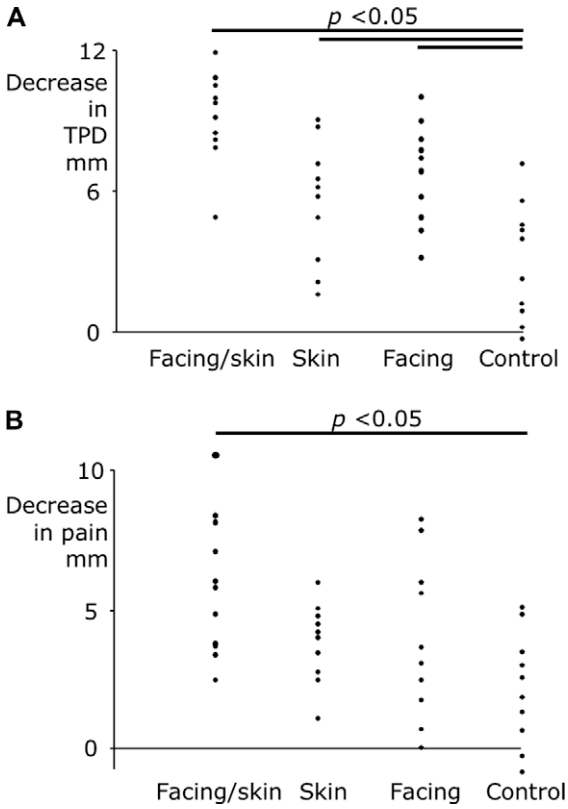

Fig. 2. Short-term effect of tactile discrimination training. (A) Decrease in two-point discrimination threshold (TPD) immediately after a single 30-min training session in each of the four conditions. Mean decrease for four sessions in each condition for each participant is shown. (B) Decrease in resting pain immediately after the session, on a 100 mm visual analogue scale (VAS).

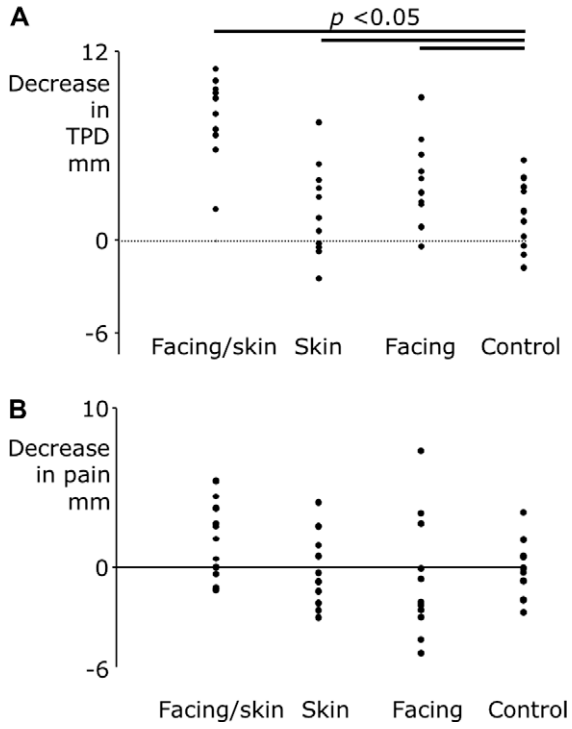

Fig. 3. Long-term effect of tactile discrimination training. (A) Decrease in TPD 2 days after training in each of the four conditions. (B) Decrease in resting pain 2 days after the session, on a 100 mm VAS.

(Fig. 2). In the Facing + Skin condition, TPD was significantly less at 2-day follow-up than at pre-session (mean [95% confidence interval] decrease = 8.0 mm [1.5–14.3 mm], $p < 0.001$) (Fig. 3).

3.2. Secondary outcome variable: resting pain

Training reduced pain (Main effect on pain of Time $F(2, 78) = 29.25$. $p < 0.001$). There was a main effect of condition on pain ($F(3, 117) = 4.69$, $p = 0.037$), but this was driven by a differential pre- and post-session effect of training between conditions (Time × Condition interaction $F(6, 234) = 8.01$, $p = 0.007$).

3.2.1. Short-term effect

Post-hoc testing revealed that pain decreased more in the Facing + Skin condition, than it did in the other three conditions ($p < 0.025$ for all, Fig. 2), but there was no difference between those conditions (n.s.).

3.2.2. Long-term effect

Post-hoc testing revealed that pain had returned to pre-session levels at 2-day follow-up (n.s.) (Fig. 3). Three participants reported that the stimuli 'occasionally hurt', but not enough to modify or cease training.

3.3. Relationship between change in pain and change in TPD

At post-session, change in pain was positively related to a change in TPD ($F(1, 118) = 261.64$ two-tailed Pearson's $r = 0.83$, $p < 0.001$), but at 2-day follow-up, it was not ($r = 0.1$, $p = 0.22$).

4. Discussion

We hypothesised that a single 30-min tactile discrimination session would impart a sustained improvement in tactile acuity if, during the training, participants looked towards the stimulated area and could see the skin of what looked like that area. The results support that hypothesis because they showed that the Facing + Skin condition led to a lower TPD threshold 2 days later, but no such effect was observed in any of the other conditions. These findings build on a wide literature concerning the effects of visuo-tactile integration on tactile performance (see [25] for review), and corroborate previous reports of enhanced real-time tactile performance in the presence of visual input in people with tactile dysfunction [24]. However, for the first time, the current results show that the effect is sustained for up to 2 days, which has an immediate clinical application. Notably, this sustained improvement in tactile acuity was achieved after a single 30-min training session. Our findings are also the first to show that the beneficial effect of visual input on tactile performance can be evoked using a mirror reflection of the non-stimulated limb.

The main new finding of this study concerns the duration of the effect. Facilitation of tactile function for at least 20 s has been shown in monkeys who were trained to associate a visual and a tactile stimulus: SI neurons remained active up to 20 s after the visual stimulus was removed [28]. Previous work also showed that in untrained healthy humans enhanced digital tactile discrimination persisted for at least 10 s after removal of visual input of the stimulated area [27] and watching, for two and a half minutes, the reflected image of one arm being touched, increases tactile sensitivity of the other arm, which is untouched and unseen, for another 3 min [23]. We confirm and extend these findings by demonstrating enhanced tactile acuity for at least 48 h after training.

How might such an effect occur? In accordance with what we know about neural changes induced by training, perhaps the effect reflects local changes in the response profile of visuo-tactile cells within S1, altered modulation of S1 neurons via bimodal or visual cells in secondary somatosensory cortex (SII) [27], or elsewhere upstream from S1 [10], for example in the parietal lobe [6]. In healthy volunteers, enhanced tactile sensitivity on one untouched and unseen hand, imparted by watching the reflected image of the other hand being touched, was ameliorated by transcranial magnetic stimulation (TMS) over the parietal cortex contralateral to the untouched hand [23]. This finding suggests that parietal lobes are important for persistent changes in sensation.

That looking towards the stimulated area also enhanced the effect suggests that spatial attention was greater during this condition than during the Skin only and Control conditions, which also implicates the parietal cortex [21]. Importantly however, we did not determine whether participants did in fact look at the reflected hand in the mirror. None-the-less, tactile stimulation alone does not improve tactile performance in peoples with CRPS [17], which further supports a role of attention in imparting a long-term effect. Regardless, as has been noted [27], because TPD threshold depends on lateral inhibition provided by interneurons in S1, a persistent change in TPD necessarily constitutes a shift in the response profile of S1 neurons, regardless of parietal or other influences.

The current study has two clear implications that have an immediate and important implication for clinical practice, beyond the management of CRPS. First, we have investigated the utility of tactile discrimination training in patients with CRPS, but we have used an approach that requires the stimuli and limb to be out of view during training [17]. This is similar to the accepted clinical practice for retraining tactile dysfunction, for example after stroke, which requires the patient to look away from the body part being stimulated [8]. The current work strongly implies that this clinical practice should be reconsidered – perhaps patients should look at the body part being stimulated. Bearing in mind that many patients do not have daily tactile training sessions, our result, that tactile enhancement at 2 days occurred only in the Facing + Skin condition, suggests that looking towards, and seeing the skin of, the stimulated body part, may make a substantial difference to

the therapeutic effect. As it applies to sensory rehabilitation in other populations, for example post stroke, tactile function is critical for functional independence, which implies that optimisation of the effect on tactile acuity is very important. The second implication is that conventional approaches to tactile training, in which patients identify stimuli they cannot see, can still be used in a manner that captures the benefits of looking towards the limb, and seeing skin of the area, via the use of a mirror. A mirror permitted patients to look towards the stimulated limb and to see the skin of what, in healthy volunteers, *looks and feels like* the limb behind the mirror [25]. This illusion may not be as strong in patients for whom the limb behind the mirror is painful, but it is also possible that some sense of agency over the reflected image may be important in the effect. We used a custom-built mirror box for this task (noigroup.com, Adelaide, Australia), but a mirror placed between the limbs may suffice. This simple clinical device would seem a workable substitute for sophisticated and comparatively expensive stimulating devices used experimentally [24].

A secondary finding of the present work was a reduction in resting pain. How might tactile discrimination training reduce pain? There are several possible mechanisms, none of which have been empirically tested. First, it is possible that tactile stimulation reflects graded exposure to sensory input, to which the sensory/nociceptive system habituates. This seems unlikely because stimulation without attention is ineffective [4,17] and the stimuli delivered in the current experiment were identical across conditions, but their effect was not. A second possible mechanism is that some conditions distracted patients more than others, although this should not reduce pain once the training is finished. Third, the effect may be related to normalisation of S1 organisation, which changes in response to tactile training [26]. There is some precedent for this possibility. For example, amputees with phantom limb pain report less pain after sensory discrimination training using electrical stimuli applied to the stump of the amputated limb. This reduction in pain correlates with normalisation of S1 reorganisation, as measured by EEG responses to stimulation of the ipsilateral lip, which is represented in S1 adjacent to the missing hand [4]. A positive relationship between pain intensity and magnitude of shift in S1 representation of the affected limb has also been reported in patients with unilateral CRPS1 [12,20]. Furthermore, and relevant to the current study, the extent of shift in S1 representation also relates positively with TPD [18]. Finally, when symptoms of CRPS resolve, S1 representation, and TPD, appear to return to normal [13,19]. Although we observed reduced pain within a single 30-min session and a strong relationship between change in TPD and change in pain, the magnitude of the decrease in pain is unlikely to be clinically important to patients and any effect was lost 2 days later.

Although there is a large amount of evidence from patients with CRPS which pain relates to the shift in S1 representation, it is not possible to determine the directionality of this relationship. Theoretical models that propose that S1 reorganisation might cause pain (for example the cortical model of pathological pain [7]), have been interrogated, but with conflicting results [14–16]. That tactile discrimination training improved TPD and pain, this improvement in TPD and pain is positively related, and that TPD relates to S1 and SII representation in people with CRPS [18], all *imply* a role of cortical reorganisation in pain, but it remains to be substantiated.

Interpretation of this study should consider several limitations. First, it is possible that the Facing + Skin condition, which used a mirror, was simply more interesting and engaging than the other conditions, which did not use a mirror – perhaps this difference imparted the extra effect. Second, we chose not to use a mirror during the Facing only condition because we wanted to keep both the hands in the same location, although this also brings with it a cost – we cannot control for effects of simply looking into a mirror. Finally, it is possible that surprise, associated with feeling but not seeing the touch on the limb contributed to the effect.

In summary, the current study demonstrated in patients with CRPS, that a single 30-min tactile discrimination session imparts a sustained improvement in tactile acuity if, during the training, patients looked towards the affected limb, but watched the skin of the opposite body part in a mirror. Looking towards the limb but not seeing skin, or seeing skin but not looking towards the limb, does not impart the long-term effect. The results suggest that current practice, not just for CRPS, but for tactile recovery after, for example, stroke, should be modified to capture the effect demonstrated here. A mirror placed between the limbs would seem an inexpensive and effective way to capture this effect.

Disclosure

The authors report no conflicts of interest.

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