Disrupted cortical proprioceptive representation evokes symptoms of peculiarity, foreignness and swelling, but not pain

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Objectives. It has been proposed that disruption of the internal proprioceptive representation, via incongruent sensory input, may underpin pathological pain states, but experimental evidence relies on conflicting visual input, which is not clinically relevant. We aimed to determine the symptomatic effect of incongruent proprioceptive input, imparted by vibration of the wrist tendons, which evokes the illusion of perpetual wrist flexion and disrupts cortical proprioceptive representation.

Methods. Twenty-nine healthy and naive volunteers reported symptoms during five conditions: control, active and passive wrist flexion, extensor carpi radialis tendon vibration to evoke illusion of perpetual wrist flexion, and ulnar styloid (sham) vibration. No advice was given about possible illusions.

Results. Twenty-one subjects reported the illusion of perpetual wrist flexion during tendon vibration. There was no effect of condition or of whether or not subjects reported an illusion on discomfort/pain ($P > 0.28$). Peculiarity, swelling and foreignness were greater during tendon vibration than during the other conditions, and greater during tendon vibration in those who reported an illusion of wrist flexion than in those who did not ($P < 0.05$ for all). Symptoms were reported by at least two subjects in each condition and four subjects reported systemic symptoms (e.g. nausea).

Conclusions. In healthy volunteers, incongruent proprioceptive input does not cause discomfort or pain but does evoke feelings of peculiarity, swelling and foreignness in the limb.

KEY WORDS: Body schema, Pathological pain, Sensory–motor incongruence, Cortical organization, Vibration, Illusion.

It has been proposed that sensory–motor incongruence can cause pain via disruption of the internal proprioceptive representation, the so-called cortical model of pathological pain [1, 2]. Data from a study in which incongruent proprioceptive (somatic and visual) feedback, imparted via limb movements either side of a mirror, evoked peculiar sensations and low level pain in some healthy subjects [2], appear consistent with that proposal. However, that paradigm relies on visual input, which makes application to conditions that involve incongruent non-visual sensory input problematic.

One way to provide incongruent sensory input without relying on visual input is via medium-frequency vibration, applied specifically to muscle tendons. Vibration at about 70 Hz stimulates muscle spindles, which in turn send information to the brain that the limb is moving [3, 4]. Simultaneous input from other proprioceptors, for example within the skin, does not corroborate that information. Thus, incongruent sensory input via vibration of the long extensor tendons of the wrist gives the illusion that the hand is perpetually moving even though the subject knows that it is not.

We have demonstrated that tendon vibration at the wrist increases the response time to recognize the laterality of a pictured hand, when the pictured hand corresponds to the hand being vibrated, but only when the illusion of wrist movement is evoked. Further, sham vibration and active and passive wrist flexion does not change reaction time [5]. Taken together, those findings suggest that the effect on reaction time to recognize hand laterality is probably mediated by disruption of the cortical proprioceptive representation of the stimulated limb. Thus, illusory movement imparted by tendon vibration permits investigation of the real-time effects of disrupted proprioceptive representation.

This study aimed to determine whether incongruent sensory input causes discomfort, pain or other symptoms in the stimulated limb. It was hypothesized that discomfort/pain would be (i) greater during vibration than during the other conditions, and (ii) greater during vibration in those who reported an illusion of wrist movement than in those who did not.

Methods

Subjects

Thirty healthy right-handed subjects (18 female) volunteered. Written informed consent was obtained and the study conformed to the Declaration of Helsinki and the National Statement on Ethical Conduct in Research Involving Humans by the National Health and Medical Research Council of Australia, and was approved by the institutional ethics committee.

Procedure

We employed a method that has been used widely to generate illusory motion of various body parts [3]. Subjects sat in front of a computer screen with the left hand held in a bracket (Fig. 1). The ulnar styloid and the tendon of the extensor carpi radialis were identified by palpation and marked with a texta. Subjects

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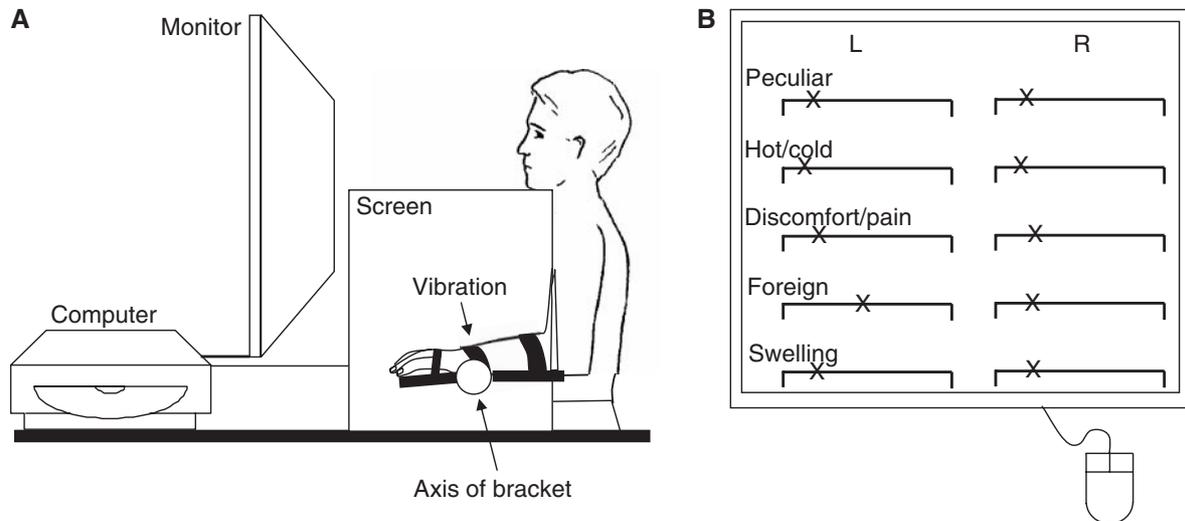
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FIG. 1. Experimental setup. (A) Seated subjects placed left hand and forearm in a bracket, which was obscured by a screen. Vibration was applied to the extensor carpi radialis (tendon vibration) or ulnar styloid (sham vibration). (B) Subject adjusted the position of the cross on visual analogue scales displayed on the monitor by moving the mouse, which was held in the right hand.

TABLE 1. Item, anchors and midpoint for each visual analogue scale that was completed in real time during each condition

Please answer the following items by placing the cross at the point on the line that best matches your experience relating to your left hand, wrist and forearm

Item	Left anchor	Middle point	Right anchor
Please indicate any feelings of peculiarity or oddness in the limb	Completely normal	A little peculiar	Very peculiar
Please indicate any discomfort or pain in the limb	Not at all painful	Uncomfortable/slightly painful	Quite painful
Please indicate any change in the temperature of the limb	Quite a lot cooler	Normal temperature	Quite a lot warmer
Please indicate any feeling of foreignness of the limb	Normal	Slightly foreign	Quite foreign
Please indicate any feeling of swelling	Not swollen	Slightly swollen	Quite swollen

were advised that they were to report any feelings in either hand, wrist or forearm, using visual analogue scales (VAS) on the screen, during each of five randomly ordered conditions. The items, anchors and middle point for each VAS are listed in Table 1. We recorded the maximum diversion from zero for items 1, 3, 4 and 5 and the maximum diversion from the midpoint for item 2. After each condition, subjects were asked to list any other feelings that they had in either upper limb, or other symptoms not confined to the upper limbs.

Each experimental condition lasted 3 min. The conditions were as follows.

(1) Control. Subjects placed their hand relaxed in a purpose-built bracket and were instructed not to move the hand.
(2) Active isometric wrist flexion. With the hand in the bracket, subject held their wrist flexed at ~20° against a small spring placed under the bracket.
(3) Tendon vibration. With the hand in the bracket, a handheld in-house vibrator (70 Hz, excursion ~3 mm) was applied to the marked location on extensor carpi radialis. Subjects were classified as 'illusion' if (i) they reported that they perceived movement at their wrist, consistent with flexion, and (ii) they did not report that movement in any other condition. If they did not satisfy these criteria, they were classified 'no illusion'.
(4) Passive wrist flexion. With the hand in the bracket, the wrist was flexed to ~45° and held in place. The subject was instructed to not try to move the wrist.
(5) Sham vibration. With the hand in the bracket, the vibrator was applied to the marked location on the styloid process of the ulnar. Subjects were classified as 'no illusion' if they reported an illusion of movement during sham vibration.

Statistical analysis

All statistics were performed using SPSS 11.0.0 (SPSS, Chicago, IL, USA). Kolmogorov–Smirnov and visual inspection of the data verified their normality, which meant that parametric statistics were appropriate. A 2 (illusion) × 5 (condition) × 5 (symptom) multivariate analysis of variance was used to detect an effect of condition or illusion on the feeling of peculiarity, temperature, discomfort/pain, foreignness and swelling in the left hand. We also undertook a bivariate correlation analysis to detect relationships between the symptoms we assessed. Bonferroni correction was applied for multiple measures such that $\alpha = 0.025$.

Results

Eight subjects did not report an illusion of movement during tendon vibration and no subjects reported an illusion of movement during any of the other conditions. Thus, there were 21 subjects classified as illusion. There were main effects of condition [Wilk's lambda $(20,415) = 0.073$, $F = 24.96$, $P < 0.001$] and illusion [Wilk's lambda $(5,125) = 0.22$, $F = 87.34$, $P < 0.001$] and a condition × illusion interaction (Wilk's Lambda $(20,415) = 0.073$, $F = 25.00$, $P < 0.001$). *Post hoc* tests showed that the left limb felt more peculiar, more foreign and more swollen during the vibration condition than during the other conditions ($P < 0.01$ for all), and for those who reported the intended illusion than for those who did not ($P < 0.022$). There was no difference in pain/discomfort or temperature between conditions ($P > 0.75$ for both) or between those who did and did not report the intended illusion ($P > 0.28$ for both) (Fig. 2). Sixteen subjects (75%) who reported an illusion
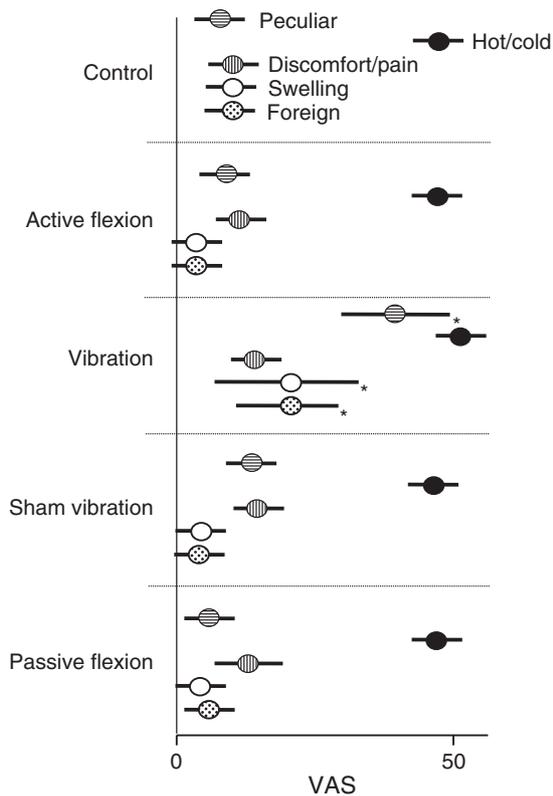
FIG. 2. Mean and 95% confidence interval for visual analogue scale (VAS) scores for peculiarity, temperature (hot/cold, VAS of 5 = normal), discomfort/pain, swelling and foreignness in the limb. *Different from all the other conditions ($P < 0.01$).
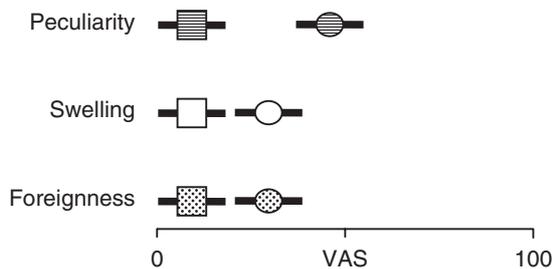

FIG. 3. Mean and S.E. (error bars) visual analogue scale (VAS) values for those symptoms that were different between subjects who reported the illusion of wrist flexion (circles) and those who did not (squares) ($P < 0.25$).

also reported peculiarity, foreignness or swelling more than two standard deviations greater than control values during tendon vibration (Fig. 3). Symptoms of peculiarity, foreignness and swelling were all related (Pearson's $r > 0.51$, $P < 0.01$ for all). There were no other relationships between symptoms. Three subjects who reported an illusion (14%) did not report any symptoms.

Other feelings in the left hand/arm were reported after each condition by some subjects, but there was no feeling that was reported by more than six subjects (20%). There were several reports of bodily feelings (e.g. dizziness) and no reported feelings in the right hand or arm (Table 2).

Discussion

The results do not support the hypothesis that discomfort/pain is (i) greater during vibration than during the other conditions,

TABLE 2. Other symptoms in the experimental (left) hand, wrist or arm and general systemic (bodily) feelings reported during each condition

	Reported feelings (number of subjects)	
Condition	In left hand/arm	Bodily feeling
Control	Itchy (3), heavy (2)	
Active flexion	Tight (3), pressure (2), shaky (2)	
Tendon vibration	Heavy (6), light (3), disconnected (3), itchy (3)	Dizzy (3), faint (1), nauseated (1)
Sham vibration	Shaky (3), tingly (2), itchy (1)	Itchy (1)
Passive flexion	Pressure (2)	

and (ii) greater during vibration in those who reported an illusion of wrist movement than in those who did not. This position is evidenced by the following results. First, there was no effect of experimental condition, or whether or not the subject reported the illusion, on the VAS for pain/discomfort. Second, there were no symptoms similar to pain or discomfort offered by subjects after the tendon vibration condition, which suggests our tools were not simply inaccurately targeted to detect an effect. Third, there was a significant effect of condition, illusion and condition × illusion interaction on other symptoms, which suggests that subjects were not simply under-reporting their symptoms.

We undertook the present study to evaluate whether, in the absence of conflicting visual information, disruption of the internal proprioceptive representation via incongruent proprioceptive input is sufficient to cause pain. That endeavour was based on the cortical model of pathological pain that proposes such disruption of the internal proprioceptive representation causes pain [1, 2]. A previous and innovative approach to this issue had healthy subjects performing bilateral limb movements either side of a mirror, such that visual feedback of one limb was replaced with visual feedback of the opposite limb, reflected in the mirror [2]. Fifteen per cent of the subjects reported mild pain when they performed opposing movements of the limbs. That is, when the arm hidden behind the mirror was moving one way (e.g. elbow flexion), the other arm, and consequently its mirror image, was moving the other way (i.e. elbow extension). The authors related this finding to motion sickness induced by conflicting visual and vestibular input, a comparison also made by Harris [1]. This finding appears to support one aspect of the cortical model of pathological pain—that conflict between sensory feedback and motor commands may cause pain. The present findings are contrary to this aspect of the model—tendon vibration induced false information about movement of the limb but did not cause pain or discomfort—but consistent with the more common finding from the study of McCabe *et al.* [2], that incongruence elicits abnormal sensations. It is possible that the vibration evoked odd feelings via central mechanisms unrelated to the illusion, for example activation of thalamic and parafascicular nuclei via the medial reticular formation, but the fact that subjects who did not report the illusion did not report symptoms suggests that this is unlikely. Thus, on the basis of the present data, the cortical model of pathological pain can be neither supported nor dismissed. Perhaps the present approach simply imparted a less powerful incongruence than that evoked by visual–sensory incongruence.

Another aspect of the cortical model of pathological pain is that sensory–motor incongruence is imparted by distorted proprioceptive representation of the limb. Although there is strong evidence that the representation of the affected limb in the primary sensory cortex (S1) is altered in people with pathological pain, for example complex regional pain syndrome 1 (CRPS1) [6], phantom limb pain [7] and chronic low back pain [8], there is little evidence that this causes a sensory–motor mismatch, certainly not of the magnitude evoked by mirror

movements. Further, when visual information is not involved, even substantial alteration of the body schema does not evoke pain or discomfort. Thus, although it seems possible that pain evoked by visual–proprioceptive mismatch indeed reflects a warning 'ominory' mechanism that generates a 'dissensory state' [2], it seems unlikely that this is mediated solely by altered cortical representation of the affected limb.

It is well established that the central nervous system detects incongruence between what is predicted to occur and what actually does occur. For example, the reafference principle states that an exact copy of the command for movement (or to not move, as was the case in the present work) is subtracted from the sensory feedback about that state [9]. There is a large amount of literature in this area, most of which is concerned with the role of detection in proprioception and motor control ([for review see 10]). However, it has also been argued that normal awareness and experience of the body is based on what is predicted until sensory feedback indicates a deviation from that prediction, in which case consciousness is alerted via abnormal sensation [11]. Our results corroborate this theory because 75% of subjects reported that the limb felt peculiar, foreign or swollen during tendon vibration and 28% of subjects reported a systemic effect, for example nausea or dizziness. The final finding raises the possibility that systemic symptoms such as nausea, which are reported by patients with pathological pain and also by those with whiplash-associated disorder, may relate to incongruent proprioceptive input rather than systemic illness.

The present results add to a growing and perplexing body of literature regarding conditions such as CRPS1. There are several aspects of this study that are directly relevant to that group—the cortical model of pain has been proposed to explain such conditions, tendon vibration evokes a similar effect on hand laterality recognition to that observed in patients with CRPS1 [12] and the symptoms evoked by tendon vibration have also been reported in this patient group. For example, CRPS1 patients perceive their affected limb to be more swollen than it actually is [13] and often report a feeling of foreignness about the limb [14]. Perhaps incongruent sensory input mediates such effects. There are certainly mechanisms documented in the CRPS1 literature that might evoke this: dysfunction of wide-diameter afferent neurons [15], cross-modality changes in sensitivity of second-order sensory neurons at the dorsal horn [16], medullary dysfunction [17], motor and sensory cortical reorganization [18, 19] and pathological processing of sensory input at posterior parietal cortex [20]. However, perceived swelling can also be evoked by anaesthesia and cutaneous stimulation [21], and a feeling of foreignness can occur after neurological injury. Thus, independent mechanisms may underpin similar symptoms.

In summary, incongruent proprioceptive input, without visual input, does not cause discomfort or pain, although it does evoke sensory disturbance in up to 75% of healthy naive volunteers. This finding does not support the cortical model of pathological pain, but, notably, does not refute it either. The symptomatic effects of tendon vibration are similar to those reported in CRPS1, which raises the possibility that incongruent sensory input may contribute to those symptoms. Further research is required to verify this possibility.

Acknowledgements

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Rheumatology	Key messages
	• Disruption of the cortical proprioceptive representation, without conflicting visual input, seems insufficient to cause discomfort/pain.
	• Consistent with proposed models of proprioception, incongruent proprioceptive input usually induces symptoms in the limb and can induce bodily symptoms such as nausea.

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