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Editorial

Sensory–motor incongruence and reports of 'pain'

McCabe and colleagues [1] investigate the hypothesis that pain without obvious accompanying tissue damage might be caused by discordance between motor intent and movement [2]. According to that hypothesis, in the same way that motion sickness might result from discordant sensory input (from vestibular apparatus and proprioceptors), pain may result from changes in the cortical representation of somatic input, which falsely signals incongruence between motor intention and movement. That the central nervous system (CNS) detects such incongruence has long been established. The reafference principle [3], whereby an exact copy of the command for movement (the 'efferent copy') is subtracted from sensory input about the actual movement ('reafference') to yield an error signal ('exafference'), and the corollary discharge model [4] are early examples. Since then, an impressive amount of research has been undertaken (see Gandevia [5] for review). However, much of this has been concerned with the role that detection of sensory–motor incongruence has in the control of movement and in proprioception, rather than in generation of pain.

Such an alternative focus seems timely. Despite rapid increases in knowledge about the genetics, molecular biology and neurophysiology of pain and the subsequent development of more targeted and effective pharmacological strategies, pain remains a continuing health problem. For example, figures from Europe, the United States and Australia suggest that about 20% of adults report chronic pain [6–8] and available treatments offer little lasting relief [9]. If we are to provide more effective treatment and management for people in pain, hypotheses such as Harris' are important. A broadened framework for understanding pain is particularly relevant for clinical situations in which pain develops when there is no demonstrable tissue damage.

McCabe and colleagues [1] set out to assess Harris' proposition about pain generation. They induced false signals of incongruence between motor intention and actual movement (or false 'exafference') by placing a mirror or whiteboard barrier between the limbs of healthy subjects while they moved their limbs. One limb was out of sight and the subject 'concentrated' on watching a fixation point placed in the middle of the barrier. McCabe *et al.* propose that when the limbs are doing different things and separated by a mirror or whiteboard, the change in visual feedback falsely signals incongruence between motor intention and movement.

The results show that when subjects watched the mirror image of one limb while they performed a different movement of the limb behind the mirror, 59% reported symptoms in an open-ended response. Notably, 15% of subjects reported low level pain during this task. Forty-one per cent of subjects reported symptoms when they performed the same movement with both limbs and ~5% reported symptoms when visual feedback was removed with the whiteboard, regardless of whether the limbs performed the same or different movements. Those results are intriguing. They support the anecdotal reports in the literature [10–12] and corroborate other reports of anomalous sensations associated with discordant sensory input, for example feeling a fake rubber hand [13]. The results support the possibility that sensory–motor discordance may evoke pain in otherwise asymptomatic people. This is important because until now anecdotal reports of an amputated, paralysed or dysfunctional hand 'coming alive', purportedly because the incongruence between motor intent and movement has been reconciled, have underpinned the use of mirror therapy in rehabilitation for conditions including stroke [14], phantom limb pain [12] and complex regional pain syndrome type 1 (CRPS1) [11, 15, 16]. At a superficial level, the results of this study support both Harris' hypothesis and the use of mirror therapy in rehabilitation. However, some caveats on the results and their interpretation should be considered.

Methodological issues make it difficult to exclude alternative explanations for the findings. For example, it is hard to remove bias in a study such as this. Subjects were related to patients, who may have been using mirror therapy; they were told that they may experience transient sensory changes, and they were asked how the tasks made their limbs feel. It is also difficult to exclude the possibility that some people experience or report symptoms in the limb simply by concentrating on it or being asked about it. Similarly, perhaps a perceived change in the limb could be evoked in some subjects just by moving it or holding it in one position. Indeed, this might be expected given the altered proprioceptive input that occurs during a sustained contraction [17]. Including a control condition, in which they simply concentrated on the limb, or a condition in which subjects just performed movements, and a condition in which subjects looked at a fixation point without the limb shielded from view, may help expose the underlying mechanisms. Perhaps also, categorization on the basis of reported symptoms may reflect variability in symptom reporting behaviour [18], or somatic awareness [19], rather than vulnerability to sensory–motor discordance. The results may also have been strengthened by increasing the duration of movements. Whereas habituation of symptoms with extended exposure would not be consistent with the hypothesis, non-habituation, or an increase in symptoms, would be consistent with it. It is notable that when healthy subjects wear prism glasses in which visual information is flipped, initial peculiar feelings subside and functional adaptation occurs quickly [20]. The time course of the sensations in the McCabe study was not described in detail, yet in order to support a specific theory involving cortical efference copies (or corollary motor discharges) in symptom generation, establishing that there was a close temporal relationship between apparent incongruence and symptoms would be critical. Finally, although primarily a qualitative study, it may have been helpful to undertake some statistical analyses, perhaps to provide an estimation of the confidence intervals regarding each class of symptom, and the presence or otherwise of systematic effects between conditions.

Several aspects of the results appear consistent with the proposed model of pain. For example, there were no other likely causes of symptoms because subjects were asymptomatic healthy volunteers; symptoms were most often reported in the condition in which discordance between motor intent and sensory feedback about the movement was greatest; symptoms faded quickly when the mirror or whiteboard, and hence the discordance, was removed. However, several aspects of the results are less consistent. About 40% of subjects reported symptoms when they performed identical movements of both limbs. Presumably there is little discordance between motor intent and perceived movement in this situation. Alternatively, small variations in movement between the limbs may be sufficiently discordant to evoke symptoms in some healthy subjects, as the hypothesis would suggest. If so, this would contradict the proposal that such a task imparts pain relief or

motor recovery in patients by removing that same discordance [11, 12, 14].

That changes in the cortical processing of proprioceptive signals cause the discordance and consequently the pain also remains to be established. It is likely that cortical reorganization occurs with chronic pain and that recovery is associated with normalized organization [21–23]. However, perhaps the pain causes the reorganization. Two findings in the literature support that possibility. First, in a magnetoencephalography study, Soros *et al*. [24] reported that pain induced in the hand via injection of capsaicin caused a decrease in the distance between the centre of gravity of the hand representation and the lip, and a decrease in the distance between the thumb and the fifth finger, both changes similar to those reported for patients with chronic pain. This group has also reported that acute hand pain can elicit phantom hand sensations in response to tactile input at the lip [25], a finding consistent with pain-induced hyper-responsiveness of the cortical hand representation to somatotopical adjacent input from the lip (see also Gandevia and Phegan [26]). Second, Birbaumer *et al*. [27] reported that regional anaesthesia of the stump in upper limb amputees with phantom pain rapidly eliminates pain and partially reverses the decrease in distance between the hand and lip representations in the primary somatosensory cortex.

Perhaps there is no causative relationship between cortical changes and pain and both are epiphenomena. Certainly both can be observed independent of the other—for example reorganization of the cortical representation of the index finger in Braille readers [28] is not associated with pain. Also, patients with CRPS1 and non-CRPS1 musculoskeletal pain show opposite changes in cortical representation [22, 29], yet both groups report pain. Considering that different pain states involve activation of different cortical networks [30], it is not surprising that the relationship between pain and cortical organization seems to be both variable and complex.

Some caution is also required when implicating particular cortical areas in the proposed production of sensations via sensory–motor discordance. For example, while the right dorsolateral pre-frontal cortex shows activity during sensory–motor conflict evoked by mirror movements [31], activity has also been observed during inhibition of action [32], imagined and executed movements [33, 34], pain [35] and itch [36]. It is likely that dorsolateral pre-frontal cortex is involved in executive/selection functions and in the monitoring of conflict between predicted and actual inputs, as are other areas such as the anterior cingulate cortex [37]. However, those cortical areas also contribute to many other functions.

The model advocated by McCabe *et al*. may apply to some pain states, but discordance between motor intent and movement seems insufficient alone to cause pain. This is supported by observations in conditions such as focal dystonia in which there can be marked changes in cortical proprioceptive representations [38], yet pain is not a clinical feature of the disorder. The point is evidenced experimentally by wearing prism glasses and more intriguingly via illusions in which body parts are falsely perceived to undergo substantial and sometimes impossible changes [39, 40]. Neither situation evokes pain.

Although the findings of McCabe *et al*. can be explained by a cortical model of pain the emphasis of which is on the motor control system, it is difficult to isolate the mechanisms to the cortex. It is also difficult to isolate the effects to the motor control system—perhaps the symptoms reported in their study reflect discordance between visual and peripheral sensory inputs. That possibility would also apply to motion sickness in which there is thought to be discordance between vestibular and non-vestibular input [41].

Caveats aside, the study by McCabe *et al*. raises important issues for the investigation of pain. Future experiments may build on the innovative approach taken by them to investigate the effects they describe in more detail. We have suggested several possible modifications that may be helpful.

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G. L. Moseley and S. C. Gandevia[1]

School of Physiotherapy, The University of Sydney and [1]*Prince of Wales Medical Research Institute and University of New South Wales, Sydney, Australia*

Correspondence to: L. Moseley, School of Physiotherapy, The University of Sydney, P.O. Box 170 Lidcombe, 1825 Australia. E-mail: l.moseley@fhs.usyd.edu.au

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