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Spatial Sensory Organization and Body Representation in Pain Perception

Review

Patrick Haggard[1,*], Gian Domenico Iannetti[2,*], and Matthew R. Longo[3,*]

Pain is a subjective experience that protects the body. This function implies a special relation between the brain mechanisms underlying pain perception and representation of the body. All sensory systems involve the body for the trivial reason that sensory receptors are located in the body. The nociceptive system of detecting noxious stimuli comprises two classes of peripheral afferents, Aδ and C nociceptors, that cover almost the entire body surface. We review evidence from experimental studies of pain in humans and other animals suggesting that Aδ skin nociceptors project to a spatially-organised, somatotopic map in the primary somatosensory cortex. While the relation between pain perception and homeostatic regulation of bodily systems is widely acknowledged, the organization of nociceptive information into spatial maps of the body has received little attention. Importantly, the somatotopic neural organization of pain systems can shed light on pain-related plasticity and pain modulation. Finally, we show that the neural coding of noxious stimuli, and consequent experience of pain, are both strongly influenced when cognitive representations of the body are activated by viewing the body, as opposed to viewing another object — an effect we term 'visual analgesia'. We argue that pain perception involves some of the representational properties of exteroceptive senses, such as vision and touch. Pain, however, has the unique feature that the content of representation is the body itself, rather than any external object of perception. We end with some suggestions regarding how linking pain to body representation could shed light on clinical conditions, notably chronic pain.

Introduction

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. This definition underlines that pain is inextricably linked to the state of one's own body. Here we focus on this somatosensory aspect of pain. We do not consider other negative experiences less obviously related to the body, such as suffering or misery.

It seems impossible to describe, or even imagine, a pain without reference to the body: disembodied pain does not make sense. But it is harder to say in what, precisely, the *embodiment*, of pain consists. All sensations are trivially linked to the body in the sense that the originating sensory receptors lie within the body; but in the case of pain, the object of the sensation appears to be the body itself. This makes a sharp contrast with most examples of visual and even tactile perception, in which the sensation ultimately contributes to perceiving an object in the external world. External stimuli may *cause* pain, but the pain itself is *about the body*, not about the external stimulus. This distinction is partly captured by the classical neurophysiological dichotomy between 'protopathic' and 'epicritic' somatosensory systems — those generating painful and tactile sensations, respectively [2]. The Greek etymology of these terms contrasts the basic interoceptive sensations of pain with the capacity of touch to support exteroceptive judgements *about* external stimuli.

Although these terms are not now widely used, we believe the distinction remains valuable, particularly for pain, as we hope to show. In our view, pain perception often has both protopathic and epicritic aspects, and therefore occupies an intermediate position between the two extremes of the classical dichotomy. Even when the stimulus eliciting a painful percept involves an external source impinging on the body surface, the *content* of pain seems to be interoceptive. At the same time, pain differs from systemic interoceptive sensations such as fatigue and hunger, because it can, most often, be felt in a very specific *part* of the body. In fact, painful sensations elicited by the activation of Aδ nociceptors, on which our review primarily focuses, seem to sit midway between protopathic and epicritic, and between interoceptive and exteroceptive sensations. To summarise, the neural systems underlying pain perception appear to have interoceptive *content*, but a spatial organization and *format* appropriate for epicritic judgement.

In this review we will show that the brain mechanisms of pain and the perceptual quality of pain are profoundly linked to the *spatial* structure of the body. Thus, representations of the body and peripersonal space are important not only for motor responses to pain, but also for functional sensory organisation of pain itself. Our spatial emphasis contrasts with the recent emphasis on affective pain processing. This tradition considers pain in relation to less spatial, more regulatory aspects of body representation within the brain [3]. We suggest that the traditional protopathic/epicritic distinction can usefully be applied *within* the cortical nociceptive pathways, because the major subdivisions of this pathway present two distinct kinds of embodiment. The insular and cingulate projections can be viewed as defining a protopathic representation of the body, which regulates distributed, non-spatial responses to pain, including autonomic and affective responses [4]. Interestingly, this system also underlies modulation of pain perception by non-specific factors such as expectation and arousal [5]. In contrast, the somatosensory and parietal projections can be viewed as an epicritic representation of the body. These projections provide coding of spatial location, with space-based registration with other sensory modalities, and with specific, spatially-organised orienting responses to pain.

[1]Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London WC1N 3AR, UK. [2]Department of Neuroscience, Physiology, and Pharmacology, University College London, London WC1E 6BT, UK. [3]Department of Psychological Sciences, Birkbeck, University of London, Malet Street, London WC1E 7HX, UK.

*The authors assert equal contributions, and have chosen to list in alphabetical order.

E-mail: p.haggard@ucl.ac.uk

Thinking about pain in terms of body representation also highlights the most important function of the nociceptive system, namely to conserve the body from actual or potential damage. Pain can trigger immediate defensive behavior, protecting the body before serious injury. Pain can also promote learning behavioural adaptations, so as to avoid situations that might produce an injury to the body. Furthermore, when an injury has occurred, pain restrains body movements and maintains specific postures to facilitate healing. Importantly, the movements necessary to adopt a defensive behaviour are precise and coordinated [6]. Thus, the motor responses to pain imply a representation of the peripersonal space around the body, and an appropriate spatial organisation of somatic sensation and motor action.

To highlight the relation between pain and the spatial representation of the body, we will discuss three main classes of evidence. First, we will consider nociceptive systems signaling different states of the body, and brain responses to transient noxious stimuli. Second, we will show how the nociceptive system interacts with other submodalities of somatosensation, so that the experience of pain depends strongly on multisensory afferent inputs. Finally, we will consider the relation between pain and the maintenance of a higher, supramodal representation of one's own body in cortical association areas, together with the potential implications of these representations for clinical conditions such as chronic pain.

In doing so, our review focuses on experimental models of pain in humans and primates. We do not cover the molecular aspects of nociception, and we focus on nociception at a system level. Finally, we focus largely on acute rather than chronic pain. The clinical literature on the effects of chronic pain on body representation is interesting, but has been extensively reviewed elsewhere [7]. Moreover, there is no satisfactory experimental human model for chronic pain, not least because the relevant experimental studies would be unethical. While several elegant studies with patients confirm associations between chronic pain and changes in the neural representation of the body [8], this literature generally struggles to distinguish between cause and effect. There are, however, some intriguing parallels between the experimental and chronic pain literatures, and the experimental results reviewed here have potentially important implications for treating chronic pain. We will discuss these in the final section of the paper.

Afferent Systems from the Body

Pain is an eminently bodily sensation. It is one of several sensations occurring following stimulation of the skin or subcutaneous tissues. Pain typically results from afferent activity in the nociceptive system, the part of the somatosensory system devoted to transmission and processing of information about noxious stimuli threatening the integrity of the body [9]. Here, we highlight the relevance of pain in relation to the body, and discuss the powerful interactions between the tactile and nociceptive systems. We revisit the classical dichotomy between a spino-thalamic system mediating crude 'protopathic' sensations about the body and a lemniscal system mediating precise 'epicritic' sensations about external objects. Although this terminology has been out of fashion [10], we will find much in it worth retaining. It may, however, best be considered as a gradient between types of somatic information, rather than a strict dichotomy between afferent systems: Aδ skin nociceptors, for example, seem to occupy an intermediate position.

Different Somatosensory Afferents Mediate Largely Specific Sensations from the Body

Discussions of sensory processing in the 20th century were dominated by the controversy between specificity ('labelled line') and pattern theories of sensory processing. Within the somatosensory systems, a large body of evidence shows that activity in specific subsets of peripheral somatosensory fibres is largely responsible for clearly distinct bodily sensations. This evidence strongly supports the specificity theory, at least at the level of primary afferents [9,10].

Nerve-block experiments demonstrate this specificity very clearly. Pressure applied to a peripheral sensory nerve results in a progressive block, progressively impairing conduction in large myelinated Aβ, small myelinated Aδ, and unmyelinated C fibres [11]. When the Aβ afferent volley is blocked, tactile sensations are abolished, while cold, pinprick pain, and burning pain sensations are preserved. When the Aδ afferent volley is blocked, pinprick pain and cold sensations are abolished, and only warm sensations and burning pain are still felt. When conduction in unmyelinated C fibres is selectively blocked by other means, such as lidocaine, thermal and painful sensations are lost, while touch is retained. This psychophysical evidence provides a strong indication that Aβ afferents mediate tactile sensations, while pain and temperature sensations are elicited by activity in Aδ and C fibres.

Further evidence for specific labelled lines comes from intraneural microstimulation of single peripheral axons. When an axon belonging to an Aβ afferent is stimulated, the type of tactile sensation depends on the receptor type. For example, a sensation of sustained pressure is elicited by stimulation of an SA-I fibre innervating a Merkel's disk, and a sensation of repetitive tapping by stimulation of a FA-I fibre innervating a Meissner's corpuscle. Crucially, the type of these tactile sensations never changes its quality — an Aβ stimulation *never* results in painful percepts — even when the frequency of stimulation is increased. Similarly, stimulation of single Aδ or C axons causes 'pure' sensations of sharp pain (Aδ fibres) or burning or dull pain (C fibres) [12], even when Aβ fibres are blocked [10]. These findings indicate that in the peripheral nervous system specific sensory channels (supplied with their own sensory organs) are activated by specific adequate stimuli [13] and mediate specific sensations, thus confirming Müller's laws of specific sense energies [14,15].

Aδ Afferent Fibres: A System in between the Protopathic and Epicritic

Peripherally, Aβ fibres have high innervation density and small contralateral receptive fields, while Aδ/C fibres have low innervation density and larger receptive fields. The central nervous system targets of Aβ and Aδ/C primary neurons also differ in many important aspects. The main central branches of Aβ afferents ascend in the ipsilateral dorsal column and make their first synapse in the dorsal medulla. The second order neurons cross the midline and ascend to the thalamus. Most of the central branches of Aδ and C afferents terminate on the ipsilateral dorsal horn of the spinal cord. Second order projecting neurons cross the midline and ascend in the contralateral anterolateral quadrant, terminating in the thalamus. Both the Aβ (dorsal

column) pathway and the Aδ/C (spinothalamic) pathway project to the primary somatosensory cortex (S1) via ventro-postero-lateral (VPL) thalamic nuclei, and to the secondary somatosensory cortex (S2) via the ventro-postero-inferior nuclei (VPI). A specific projection to the posterior insula via the posterior part of the ventro-medial nucleus (VMpo) has been suggested as a thalamic relay for pain and temperature pathways [16–20], although this has been the subject of controversy [21,22].

These psychophysical and anatomical observations lead to a classical dichotomy, originally formulated by Head, between 'protopathic' sensations mediated by the spinothalamic system and 'epicritic' sensations mediated by the dorsal column system [2,23]. This dichotomy is certainly valid when considering the precise tactile sensations mediated by Aβ mechanoreceptors (stimulated, for example, by the manipulation of objects) and the crude thermal and painful sensations mediated by C polymodal nociceptors (stimulated, for example, by intense changes of body temperature). However, experimental evidence reviewed here suggests that the painful sensations mediated by the activity of Aδ nociceptors should not be considered entirely protopathic, but functionally closer to those mediated by tactile stimuli activating Aβ mechanoreceptors.

Indeed, Aδ nociceptors exhibit a higher stimulus specificity than polymodal C nociceptors. For example, type I Aδ mechano-heat units (I-AMH) respond preferentially to noxious mechanical stimuli, while type II Aδ units respond preferentially to noxious thermal stimuli [24]. Although the preferential response of Aδ nociceptors does not reach the absolute stimulus specificity of Aβ tactile receptors, it is reminiscent of the observation that mechanoreceptors respond only to their adequate stimulus type, at least at lower energy levels. In striking contrast with such stimulus specificity of Aδ and Aβ afferents, unmyelinated C fibres dramatically adjust their function when they are severed and forced to innervate a new type of tissue. This is achieved by altered expression of neuropeptides released at central synapses [25]. This indicates that C fibres provide specific information about the body territory they innervate. As discussed below, impairing their function dramatically changes the perceived size of the innervated body territory [26]. Furthermore, as detailed below, the spatial precision of somatosensory perceptions elicited by Aδ-fibre stimulation is much better than that of perceptions elicited by C-fibre stimulation, and more similar to that of Aβ fibres [27,28].

Multimodal Brain Responses to Nociceptive and Non-nociceptive Stimuli

Pain, like any other conscious experience, is the result of cortical activity [15]. Several studies have used functional brain imaging techniques, which provide *in vivo* information about the cortical activity elicited by noxious stimuli. Neuroimaging techniques such as EEG and fMRI are *population* measurement methods, reflecting the mass activity of large numbers of neurons [29,30], so caution is required when drawing conclusions about specific neural codes from such methods.

The EEG and fMRI responses elicited by transient noxious stimuli originate from an extensive network of brain regions (the so-called 'pain matrix') that is often considered to reflect the neural activities mediating pain experiences [31–35]. Interestingly, some early reports already suggested the possibility that these responses could also be due to the alerting or arousing consequences of pain [36–38]. In fact, unexpected, intense but non-painful visual, auditory or somatosensory stimuli elicit cortical responses extremely similar to the so-called 'pain matrix' responses elicited by noxious stimuli (Figure 1) [39,40]. This indicates that, at least at the macro scale of the current techniques for sampling the activity of populations of neurons *in vivo*, the EEG and fMRI responses elicited by transient noxious stimuli are largely not, in fact, nociceptive-specific. Rather, they reflect the activity of a neural system involved in detecting, orienting attention towards, and reacting to the occurrence of salient sensory events. Interestingly, electrophysiological studies in non-human primates have identified neurons in premotor and parietal areas that detect multimodal threats (i.e. they respond to both nociceptive and threatening visual stimuli close to their somatosensory receptive field) [41–43] and whose stimulation produces defensive behaviors [6,44].

Thus, this cortical network responding to transient nociceptive stimuli in humans might represent a basic mechanism through which significant events for the body's integrity are detected, regardless of the afferent sensory channel. Interestingly, the only macroscopic difference in the EEG and fMRI response elicited by somatic (nociceptive and non-nociceptive) and non-somatic stimuli (auditory and visual) was located in the S1 and in small portions of the S2 [40]. Crucially, such activity was *somatosensory*-specific — it was equally triggered by stimuli delivered to the body, perceived as either painful or tactile — but it was not nociceptive-specific. This observation highlights a striking similarity of the EEG and fMRI responses elicited in somatosensory areas by nociceptive and non-nociceptive stimuli.

Somatosensory-specific Brain Responses to Nociceptive and Non-nociceptive Stimuli

Traditional fMRI analyses can show increased signal in specific brain areas in response to sensory stimulation, but can not establish causal relationships. Instead, dynamic causal modelling has been used to explore how nociceptive and non-nociceptive somatosensory information flows within the somatosensory system. Dynamic causal modelling estimates the effective connectivity between different brain areas [45], and tests a specific set of hypotheses, defined *a priori*. Dynamic causal modelling of human fMRI data has been used to test whether the cortical processing of non-nociceptive input in S1 and S2 is serial or parallel, and whether the organization of nociceptive and non-nociceptive somatosensory processing in S1 and S2 is different [46]. The neural activities elicited by both nociceptive and non-nociceptive somatosensory stimuli were best explained by models in which the fMRI responses in both S1 and S2 depended on direct thalamocortical projections, indicating that both nociceptive and non-nociceptive information are processed in parallel in S1 and S2.

Topographic maps of the receptive surface are a fundamental feature of sensory systems, although the functional advantage that such maps confer is far from being understood [47]. Maps of gross body segments — for example, face, hand, trunk, foot — have been clearly described in response to both innocuous and nociceptive stimuli at different levels of the somatosensory system, including the dorsal horn, the thalamus, SI and SII [48–53]. In contrast,

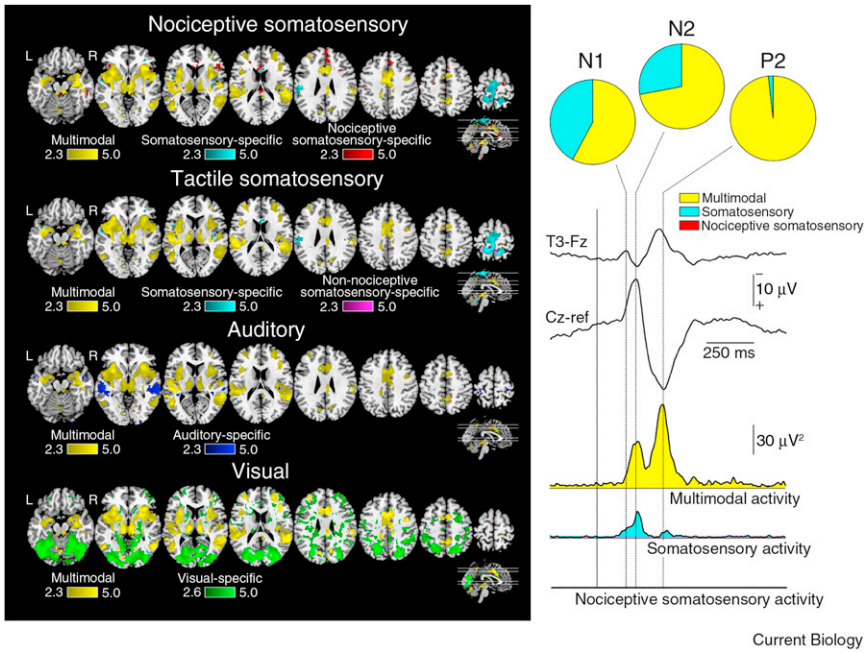

Figure 1. Unimodal and multimodal neural responses to sensory stimuli.

Left panel: Conjunction analyses of the BOLD fMRI responses elicited by transient stimuli of four modalities (pain, touch, audition, vision). Random-effect group analysis, voxel threshold Z > 2.3 and cluster threshold p < 0.05, corrected for multiple comparisons across the whole brain. Voxels responding to all four types of sensory stimuli are shown in yellow. Voxels uniquely responding to stimuli delivered to the body (either nociceptive or non-nociceptive) are shown in cyan. Nociceptive-specific voxels — voxels displaying significant activation only to nociceptive somatosensory stimuli — are shown in red. Note the large amount of spatial overlap between the responses elicited by all four modalities of sensory stimulation. (Adapted with permission from Mouraux *et al*. [40].) Right panel: multimodal and somatosensory-specific activities contributing to nociceptive-evoked EEG responses (laser-evoked potentials, LEPs). LEPs appear as a large negative-positive biphasic wave (N2–P2), maximal at the scalp vertex (shown here at Cz versus nose reference). An earlier negative wave (N1) precedes the N2–P2 complex. The N1 (shown here at T3 versus Fz) is maximal over the temporo-central area contralateral to the stimulated side. The greater part of the LEP waveform is explained by multimodal brain activity (that is, activity also elicited by stimuli of other sensory modalities). The time course of this multimodal activity, expressed as global field power (μV2), is shown in gray. Note how multimodal activity explains the greater part of the N1 and N2 waves and almost all of the P2 wave. Somatosensory-specific brain activity (i.e., activity elicited by both nociceptive and non-nociceptive somatosensory stimuli) also contributes to the LEP waveform. The time course of somatosensory-specific activity is shown in black. Note how its contribution is largely confined to the time interval corresponding to the N1 and N2 waves. Note also the lack of nociceptive-specific somatosensory activity contributing to the LEP. (Adapted with permission from Mouraux and Iannetti [39].)

fine-grained topographic representation of single digits within SI has been repeatedly described in response to tactile, but never to nociceptive stimulation [54–56]. We recently combined the selective stimulation of Aδ and C nociceptive afferents using laser stimuli [57] with a phase-encoding fMRI mapping technique [56], and discovered nociceptive somatotopic maps of single digits in the SI contralateral to the stimulated hand [58].

These nociceptive maps are highly aligned with maps of the responses to Aβ stimuli. This observation is in striking contrast with data on the innervation and receptive field size on the fingertips. Mechanoreceptors have extremely high innervation density and small receptive fields, which provide the exquisite spatial acuity for touch. In contrast, the density of pain-related epidermal fibres in the fingertips is remarkably low [59,60]. However, we recently observed that the spatial acuity for pain is nevertheless higher on the fingertips than on proximal body territories, and that this distal-proximal gradient is comparable to that for touch. This 'fovea' for pain on the fingertips cannot readily be explained by innervation density of pain-related fibres. Thus, this finding implies that the afferent systems transmitting information resulting in pain and touch sensations powerfully interact in the central nervous system, possibly at the level of SI where fine-grained maps of both nociceptive and non-nociceptive inputs are present.

Several studies have investigated the ability to localize pain using a variety of psychophysical methods [27,61–63]. However, this literature is complicated by the diversity of methods for measuring localization. Studies of tactile localization have drawn an important distinction between measures of acuity (such as the Grating Orientation Threshold; [64]), and of hyperacuity [65]. Acuity corresponds to the fundamental spatial precision of a single receptive field, while hyperacuity corresponds to the best spatial precision that can be achieved by integrating responses of a population of several receptive fields. Some widely used somatosensory tests, such as tactile two-point discrimination thresholds, and simple localization of stimulus location on the skin, involve an unknown mixture of both these two forms of coding. To our knowledge, no study has yet reported separate estimates of acuity and of hyperacuity for nociceptive stimulation.

Moreover, the neural substrate of pain localization remains unclear. There is a natural tendency to assume that topographic maps, such as those in S1, underpin pain localization. The evidence for this is equivocal, however, as neuroimaging studies provide only correlational evidence, and not causal evidence. Intracranial stimulation studies provide evidence for a gross somatotopic map in the posterior insula, and suggest a causal role in pain localization [66,67], which was recently confirmed by fMRI in healthy volunteers [52]. However, the precision of such insular maps seems very low, and not sufficient to explain the observation that the ability to localize pain approaches the ability to localize touch [27,28]. Porro *et al.* [68] reported that transcranial magnetic stimulation (TMS) over S1 impaired localization of a noxious mechanical stimulus, thus suggesting a causal role of S1 in spatial localization of pain, but we recently found no effect of S1 TMS on localization of a nociceptive-specific laser stimulus [69]. Further studies are required to conclusively demonstrate that

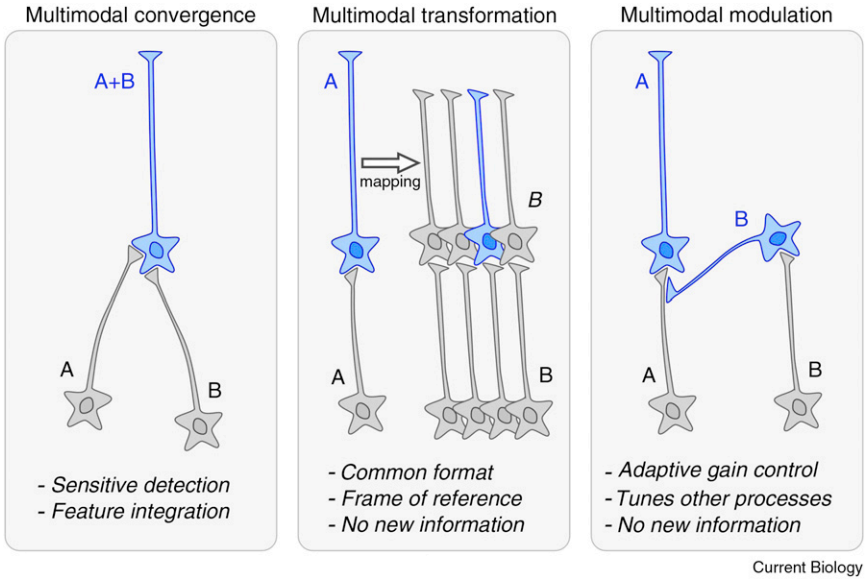

Figure 2. Three forms of multisensory interaction.

In *multimodal convergence*, afferents carrying information in two distinct modalities converge on a single higher-order neuron. The higher-order neuron now responds to stimulation in either modality, and is thus "bimodal". In *multimodal transformation*, information in one modality is transformed into a frame of reference given by the organization of another modality's afferent pathway. In *multimodal modulation*, information in one modality is used to change synaptic connections in the afferent pathway of another modality.

nociceptive maps in S1 are causally responsible for pain localization ability.

Altogether, these results indicate a specific role of S1 in processing bodily stimuli. The functional significance of such similar activities elicited by both nociceptive and non-nociceptive stimuli in SI is still far from being understood, but it suggests a clear anatomo-functional substrate for powerful physiological interactions between pain and touch.

Interactions between Pain and other Somatosensory Submodalities

The previous section has considered the afferent pathways that carry nociceptive information. In the periphery, these pathways display a clear nociceptive specificity, but there is progressive integration with other modalities at higher stages. This section focuses on the mechanisms that link nociceptive input to other somatosensory signals, and thus bring pain sensation clearly into the context of the body. We make an important distinction between inter-sensory interactions that relate specifically to body representation, and other, more general forms of interaction, such as arousal. For example, while chronic pain is commonly associated with reduced tactile sensitivity on the affected part [70,71], acute pain has been found to facilitate the perception of touch [72]. But as this effect was independent of the relative positions of the nociceptive and tactile stimulation, the authors interpreted it as a general alerting effect, rather than a specific somatosensory interaction. Similarly, acute pain has repeatedly been shown to inhibit persistent pain, in the so-called diffuse noxious inhibitory control effect [73,74].

The diffuse noxious inhibitory control effect does not merely reflect distraction, because it occurs in anaesthetized rats [75], and because it occurs independently of the effects of simultaneous distractors in human volunteers [76]. However, the location of the acute pain does not influence the diffuse noxious inhibitory control, suggesting that it does not strongly involve representation of the body. To link pain specifically to body representation, rather than just to non-body-specific effects of sensory stimulation, the spatial specificity of the interaction is key. We discuss the frame of reference of these spatial interactions below.

Computational Framework for Nociceptive–non-nociceptive Interactions

From a computational viewpoint, multisensory interactions, such as those between nociception and other somatosensory modalities, can be grouped into three different classes, corresponding to three quite distinct information-processing functions (Figure 2).

First, information from two different modalities can be *integrated* by simple feedforward convergence onto a single higher-order neuron. Physiologically, integration involves synaptic summation of excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs). Computationally, feedforward convergence may contribute to optimal integration of different kinds of information about the same object [77,78]. Second, information in one modality can be *transformed* or reformatted into a map or reference frame defined by another modality. Third, information in one modality may be *modulated* by another modality. The modulatory connections may be horizontal, from other signals at the same level, or may be vertical, top-down modulation by which higher areas can control their own input. The modulation may also be inhibitory or excitatory in nature.

Computationally, multisensory modulation involves one input providing a gain-control mechanism for a second afferent pathway. In the following sections, we review evidence for integration, transformation and modulation of nociceptive and other somatic signals, with the aim of understanding how processing of pain is linked to the perception of the body.

Bimodal Nociceptive Neurons?

Both convergence and integration seem at odds with the textbook picture of the somatosensory system, which stresses the segregation of nociceptive and mechanoreceptive afferent pathways (see above). One hallmark sign of convergence between nociceptive and other somatic signals would be a bimodal neuron responding to either a nociceptive or a non-noxious input, particularly a non-noxious input in a different submodality. The wide-dynamic range neurons in the spinal cord [10] have this property. Further, many studies have reported mechanoreceptive neurons in S1 which also respond to the temperature of a mechanical stimulus. These are found both in classically 'tactile' areas 3b and 1 of S1 [79], and also in the classically proprioceptive/nociceptive area 3a [80]. Further, the relation

between stimulus intensity and firing rate in some of these neurons suggests that they may be related to perception of pain intensity [81].

It remains unclear whether such neurons with both mechanoreceptive and thermal nociceptive responses meet the formal criteria for bimodal multisensory integration [82]. These criteria require comparing the response to each stimulation of each modality separately with the response to combined stimulation in both modalities, but many single-unit recording studies of combined mechanoreceptive and nociceptive responding have used contact-heat stimuli. Such stimuli inevitably involve both thermal and mechanical stimulation, so the unimodal response to thermal input without touch cannot be characterized [41]. Therefore, these neurons cannot (yet) be definitively described as implementing multisensory convergence or integration.

Only a few studies have used invasive electrophysiology to measure the responses of single nociceptive neurons in somatosensory areas to nociceptive-specific (for example, laser) stimuli [83]. These studies did not systematically assess responses of the same neurons to other modalities. Therefore, we know of no evidence of single units integrating nociceptive and other bodily inputs, according to the standard criteria for multisensory integration [84]. In particular, it remains unclear whether nociceptive inputs are integrated with other sensory information by intraparietal [85] and premotor [86] neurons. Neurons in these areas perform multisensory integration based on vision and touch, providing a representation of the body surface and peripersonal space. Certainly, neurons in area 7b respond both to thermal noxious, non-noxious mechanical and even threatening visual stimuli approaching their somatosensory receptive field [41]; however, this study did not formally test whether these neurons' firing represents an integration of the component inputs, rather than a simple summation, and did not test nociceptive-specific responses in the absence of touch. Nevertheless, the picture emerging from this study is of pain participating in a multimodal system for attending to and escaping from threat, rather than being an isolated perceptual system.

In contrast, many studies that measured *population* neural activity have reported interactions between nociception and other somatic submodalities, notably touch. Existing single-unit recording approaches cannot readily distinguish between integration of two types of signals into a single code, and modulation of processing for one type of signal by the presence of a second signal. Given this ambiguity, we distinguish these two kinds of interaction on computational grounds, as shown in Figure 2. When interaction between pain and other bodily sensations can be interpreted as convergence on a single representation of a cross-modal perceptual object, integration seems the most plausible interpretation. Interactions that appear more like regulatory gain control are discussed in the modulation section.

We suggested in our introduction that perceptual systems for pain might be special because their content was the body itself, rather than any external object. However, some studies suggest that pain–touch integration can also contribute to representing external objects. In a series of recent studies, perception of temperature on the digits was biased by tactile input [87,88]. Thus, when three adjacent fingers were touched, the surface temperature perceived by the central finger was attracted towards the perceived temperature of the two outer fingers. This pattern of results is consistent with the view that the brain first integrates tactile and thermal information, and then applies the perceptual constraint that all three fingers contact a single object with a common thermal energy level.

In these studies, the temperatures involved were not in the nociceptive range. However, this observation is clearly reminiscent of the thermal grill illusion, in which a cold surface touched by a central finger is in fact felt as painfully hot, when the two outer fingers touch a warm surface [89]. Neuroimaging studies showed that the illusion was associated with activation of the anterior cingulate cortex — an area important in the detection of threatening and salient events. This suggests that the stimulation, while actually non-noxious, was processed in brain areas important for responding to pain [90]. The thermal grill illusion is generally explained as an unmasking of heat-responsive C-fibre input. The illusion operates over relatively large spatial scales [91], with spacing of up to 30 cm between the hot and cold points. However, we recently showed that the illusion itself does not require a strong mechanoreceptive input: simply immersing the fingers in liquids at appropriate temperatures was sufficient to produce an illusion of heating approaching the pain range, and the illusion even persisted for some minutes after the fingers were removed from the liquid [92].

Interestingly, however, the same study also provided evidence for a role of the body as a cross-modal perceptual object in integration of nociceptive stimuli [92]. We found a strong reduction in perceived heat when participants touched together the fingertips of their two hands which had both been pre-exposed to the thermal grill pattern. The correlation of thermal and tactile input across the two hands influenced activity in the nociceptive system. Self-touch provided a situation where the body itself became the *object* of both tactile and thermal perception, with a strong influence on the latter. This effect may involve both modulatory and integrative mechanisms.

Mapping of Pain Signals into External Space: Somatotopic and Spatiotopic Nociception

A general principle of multisensory processing holds that the brain remaps multiple sensory signals into a common reference frame, in order to allow a single appropriate motor response, such as orienting towards the source of stimulation [93]. For example, information about the location of a stimulus on the body surface is combined with signals about the spatial configuration of the body to compute the location of the stimulus in external space. Tactile stimuli are 'remapped' within 180 ms, so that they participate in multisensory interactions based on their location in external space, rather than their location on the body surface [94]. This remapping process occurs in the intraparietal areas of the human brain, where proprioceptive information about the position of the limbs is combined with tactile information about stimulus location on the skin. Combining these two sources of information allows the brain to transform somatotopic to spatiotopic coordinates [95]. Specifically, TMS over the presumed human homolog of the ventral intraparietal area impaired the integration of tactile and proprioceptive information required to localise tactile stimuli in egocentric external space [95].

This transformation was held to be important also for the organisation of orienting responses, such as defending the body surface [96] and scratching a site of irritation [97].

One might therefore imagine that signals relevant to pain, such as touch, would be remapped according to the current position of the body in space. Surprisingly few experimental studies have addressed this question, and these tend to report spatiotopic effects on pain. Gallace and colleagues [98] reported that crossing the arms reduced the perceived intensity of a noxious laser stimulus. As there were no changes in the early components of the laser-evoked EEG potential, notably those associated with the afferent input reaching the primary somatosensory cortex [99], they interpreted their effects in terms of a transformation from somatotopic to spatiotopic frame of reference in higher cortical areas, similar to that reported previously for touch [95]. However, the reduction in pain intensity associated with crossing the arms suggests that this remapping may be imperfect.

To our knowledge, no other studies have investigated the integration of pain-related activity within somatotopic frames of reference or peripersonal space. However, the alerting value of pain, and the need for defensive reactions to prevent tissue damage, suggests that pain-related signals should be rapidly transformed into external spatial coordinates, just like other non-noxious stimuli with alerting or defensive value [100]. The spatial organisation of nociceptive signals and pain sensations will be a fruitful field for future research. As a first hypothesis, we suggest that the spatial organisation of pain *expectation* may differ sharply from that for pain *perception*, because of the different roles that these processes play in *responding* to pain. When painful stimulation is expected, but has not yet occurred, the need to prepare evasive or defensive motor actions or reactions may dominate. These actions require a spatial organisation based on the same egocentric reference frame used for other actions such as orienting responses such as reaching [101].

After painful stimulation has been received, however, the interaction with the motor system changes dramatically. If the stimulus is very brief, motor action can no longer influence the stimulation directly. In other cases, the stimulus itself may trigger a reflex withdrawal response to move away from the source of exposure. In both cases, higher motor centres may not need a spatiotopic code for pain, and somatotopic coding of pain may return. This hypothesis could be explored in future studies varying the time interval between painful stimulation and arm movements. In summary, the remapping of pain perception into spatiotopic coordinates may be simply a byproduct of the planning of orienting responses by the cortical motor areas.

Modulation of Nociceptive Signals by Other Somatic Signals

The hallmark sign of multisensory modulation is that the intensity of one signal varies with the presence or absence of a signal in another modality. Importantly, there is no change in sensory quality of the first signal, thus distinguishing modulation from other phenomena such as intersensory substitution or synaesthesia.

The gate control theory of pain refers to multisensory modulation of this kind. Melzack and Wall [102] suggested that small fibre nociceptive pathways responsible for signaling pain were inhibited by concomitant large fibre inputs signaling touch. The use of self-touch to reduce pain sensation discussed above [92] may be an interesting example of a behavioural adaptation taking advantage of gate control. Melzack and Wall located the gating interaction in the spinal cord, and also emphasised the importance of descending control in 'closing the gate' to reduce sensations of pain resulting from peripheral small-fibre input. A full review of this extensive literature is beyond our scope. However, the principle of gating seems to apply pervasively to interactions between touch and pain at several levels of processing, including the thalamus and cortex, as well as the spinal cord.

Green and colleagues [103,104] identified a specific class of nociceptors demonstrating the classic gating pattern of touch inhibiting pain. However, the pattern of this interaction depends importantly on representing the state of one's own body. Stimulation of multiple small sites on the skin with warm and cold stimuli produced painful sensations, even at moderate, non-damaging stimulus temperatures [103]. This interaction confirms the close link between thermoception and pain proposed by Craig [19]. The distribution of these sites was sparse and spot-like [103], recalling the classical reports by Rivers and Head [2] of a mosaic of isolated thermal sensations on the skin. Importantly, these sensations were strongly inhibited by mechanoreceptive input, as they were more readily evoked with smaller than with larger contact probes [103]. Most interestingly for our purpose, the interaction between touch and thermoception depended on the *nature* of the tactile stimulus. 'Dynamic' stimulation, obtained when the probe arrived in contact with the skin, inhibited the nociceptive sensations to a greater extent than sustained, 'static' contact [105,106]. Conversely, sustained light touch could produce nociceptive sensations at temperatures that are normally considered non-noxious. Green interpreted this difference as an example of sensory attribution: painful sensations immediately following a tactile onset are attributed to the thermal energy level of the tactile object itself.

When we contact a very hot or very cold object, defensive reflexes cause withdrawal from the object, and avoid tissue damage. In contrast, prolonged thermoceptive input in the *absence* of tactile onset may be attributed to a change in one's *own* body temperature. This is potentially much more serious to the organism, and cannot be redressed by simple reflex responding. For our purposes, when a tactile onset is present, pain may be 'about' the touched object, but when no tactile onset is present, pain may be 'about' the body. Thus, the same afferent signals may have both an interoceptive, more protopathic function, and an exteroceptive, more epicritic function. The contribution of each of these aspects is not a hard-wired feature of the afferent pathway, but a result of the stimulation profile, and of how the stimulation is interpreted centrally. This series of studies both provides a well-studied example of inhibitory modulation, and also an important window into the intentionality of pain. In particular, this literature shows that pain, like other sensory inputs, must face the computational challenge of attribution: assignment either to the self, or to an external pain-inducing object.

Neuroimaging studies have investigated pain-touch interactions within the brain. Here, an important concern is to distinguish interactions at the cortical level from the segmental interactions suggested by the gate control theory. We assume that the integration of pain processing within an overall representation of the body requires a cortical, rather than a spinal interaction. Inui and colleagues [107] investigated the temporal specificity of the touch-pain interaction. Intra-epidermal electrodes were used to selectively stimulate Aδ fibres, and produce a pricking pain sensation.

A transcutaneous shock, activating primarily Aβ fibres, was used as a conditioning stimulus. When the Aβ stimulus was given 0–500 ms before the Aδ stimulus, pain ratings for the Aδ stimulation and responses measured with MEG from primary and secondary somatosensory cortices were both significantly reduced. The time-course of the reduction was interpreted as showing that the interaction occurred at cortical, rather than at spinal levels. An earlier study [108] showed that continuous mechanical vibration reduced both perceived intensity of pain and amplitudes of laser-evoked potentials. This provides a stronger demonstration of touch–pain interactions, but cannot distinguish whether it occurs at a spinal or a cortical level.

In general, although touch–pain interactions have been extensively investigated at the molecular and segmental levels, surprisingly few studies have considered this interaction in the context of representations of the body. For example, how does the spatial separation between a tactile and a nociceptive stimulus influence the ability of touch to modulate pain? Is the spatial parameter relevant for touch–pain interaction defined on the skin, somatotopically, or in external space, spatiotopically? Finally, do the multisensory cortical regions that maintain representation of the body and of peripersonal space, such as the IPS areas in humans, and VIP in monkeys, contribute to these touch–pain interactions?

A recurrent difficulty arises from the multiple levels of interaction between somatosensory submodalities. For example, the gate control theory [102] emphasises tactile suppression of nociceptive signals in the spinal cord. These segmental changes result in altered afferent input to the cortex, and would therefore lead to 'inherited' changes in all subsequent cortical processing. This makes it difficult to distinguish between low-level nociceptive interactions, and involvement of more cognitive representations of the body, for example in the parietal cortex.

An alternative approach involves studying sensory modalities that, as far as we know, do not interact segmentally. In these cases, a more central mechanism of interaction between pain and other body-related information may be involved. For example, clinical studies have shown that chronic post-stroke pain can be reduced by caloric vestibular stimulation [109]. This interesting finding was originally attributed to a vestibular activation of the posterior insula, leading in turn to an inhibition of the anterior cingulate cortex. That is, the interaction was not attributed to reflect modulation in somatosensory areas. However, we have recently discovered an interaction between vestibular stimulation and pain *perception* occurring at early somatosensory levels [110]. During caloric vestibular stimulation, the pain threshold for a contact heat probe on the hand dorsum was significantly increased. The possibility of a tactile gating contribution to this effect was ruled out by demonstrating, in a control experiment, that nociceptive stimulation delivered without contact using a laser showed the same analgesia during vestibular stimulation. The vestibular stimulation was designed to activate primarily the right hemisphere, but the change in pain threshold was found on both hands, suggesting it arises in a brain area characterised by bilateral representation.

Measures of somatosensory evoked potentials demonstrated an interaction between vestibular and non-nociceptive somatosensory input generated by median nerve stimulation. The components affected were localised to the early somatosensory cortex (probably area SII) [111]. As these somatosensory cortical areas are also activated by nociceptive inputs [112], it seems likely that vestibular signals may also modulate nociceptive processing in early somatosensory cortex, though direct evidence is so far lacking. The functions of such vestibular-nociceptive interaction remain unclear. In the world outside the laboratory, vestibular activation accompanies every orienting movement towards a novel environmental location. Vestibular input may adjust cortical processing both for one's own body and for the external environment, in a form of multisensory rebalancing.

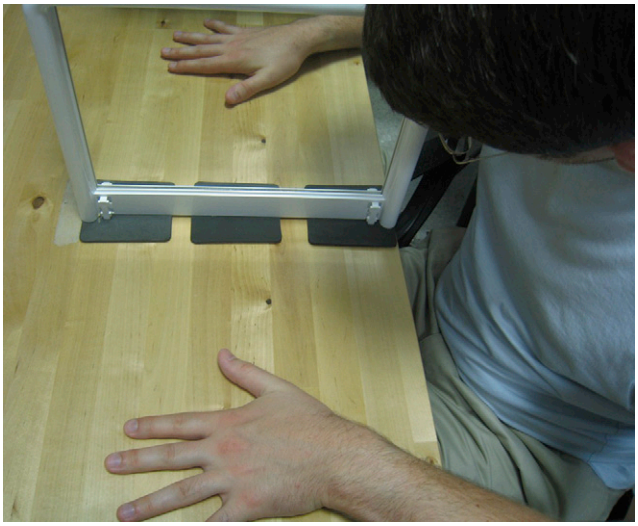

Figure 3. The mirror-box illusion.

A mirror is placed parallel to the participant's body midline, such that the mirror image of their left hand appears to be their right hand, and to occupy the felt position of the right hand. While originally introduced by Ramachandran and colleagues as a method to allow amputees to 'see' their phantom limb, the mirror box is a powerful visual illusion in healthy participants as well. The illusion allows the visual experience of the body to be manipulated, while keeping vision entirely non-informative about somatosensory stimulation.

Pain and Higher-level Body Representations

The preceding section discussed modulation of pain by other somatosensory modalities. Here we discuss interactions between pain and higher-level *representations of* the body: we will argue that these can be distinguished from interactions between nociception and other *somatosensory signals from* the body [113].

Visual Analgesia

We recently found that the specific content of vision also modulates the experience of pain. In our first experiment, we used a mirror box to create the illusion that participants were looking directly at their stimulated hand, while ensuring that vision was completely non-informative about stimulation (Figure 3). Seeing the hand produced a clear analgesic effect on acute laser pain compared to seeing a non-hand object [114]. This visual analgesia was apparent for subjective ratings of both perceived pain intensity and unpleasantness, and also for the amplitude of the N2/P2 complex of laser-evoked potentials. Importantly, this effect was specific to seeing one's own hand: seeing the experimenter's hand had no apparent effect, suggesting it is specifically related to self-perception. This provides an

intriguing contrast to work on empathy for pain. Empathy for pain shows clear interpersonal links [115,116] and modulates activation of 'affective' nodes of the cortical pain network, such as the insular and cingulate cortices [117].

We subsequently extended this result by investigating heat pain thresholds. Seeing the body not only reduces pain but can even determine whether or not a particular stimulus is felt as painful in the first place, by increasing contact-heat pain thresholds [118]. A generalization of this result came from Hänsel and colleagues [119], who used a whole-body analogue of the rubber hand illusion. They found that seeing a mannequin touched while being touched oneself increased pressure pain thresholds, whereas seeing a non-body object touched had no such effect. Further, the magnitude of this change was positively correlated with participants' reported self-identification with the mannequin.

These modulations show that the specific visual context of one's own body alters the sensory processing and conscious experience of pain. Further, this relation seems to be proportional, and obeys a cross-modal magnitude relation: visual illusions that alter the perceived size of the body can also alter the perceived intensity of pain. Mancini and colleagues [118] fitted a mirror box with magnifying and reducing mirrors, to create the feeling that one's hand was either larger or smaller than its true size. They first reproduced the visual analgesia associated with viewing the hand rather than a neutral object. Further, minimizing the perceived size of the hand reduced visual analgesia, while magnifying the hand boosted it. This result parallels modulations of chronic pain from visual distortions of body size. In unilateral complex regional pain syndrome (CRPS) patients, visual magnification increased pain, while visual reduction decreased it [120]. Similarly, visually-induced illusions of stretching or contraction of body parts reduced arthritic pain [121]. Intriguingly, in that study, only distortion of the chronically-painful finger produced this effect, while distortion of the entire hand did not. This confirms the impression that spatial specificity is a key feature of pain–body interactions.

We have recently investigated the analgesia associated with viewing one's body using fMRI. Viewing the hand reduced activations due to laser stimulation in both ipsilateral primary somatosensory cortex and operculoinsular cortex [122]. Further, the visual context of seeing the body led to increased effective connectivity (functional coupling) between the putative 'pain matrix' and a network of posterior brain areas related to vision of the body ('visual body network'), including the superior parietal cortex and occipito-temporal areas. Importantly, the areas showing reduced activation to pain when seeing the hand were only a relatively small subset of the wide network areas showing increased connectivity with the visual body network. Considering that the large part of the cortical response to a transient laser stimulus reflects stimulus detection and not pain perception [123,124], this result suggests that rather than simply dampening the ability to detect the stimulus, seeing the body could qualitatively change the nature of pain.

What causes visual analgesia? One possibility is that visual analgesia may be driven by increased intracortical inhibition in the somatosensory cortex. Several pieces of evidence support this interpretation. First, several forms of chronic pain are associated with reduced inhibition in sensorimotor cortex [125–127]. Further, interventions that enhance intracortical inhibition, such as GABA agonist drugs [128] and repetitive TMS to motor cortex [129], are effective treatments for chronic pain. Such results suggest that interventions which increase local introcortical inhibition in somatosensory cortex may result in analgesia. Second, in addition to reducing pain, vision of the body is also known to increase the spatial sensitivity of touch [130,131]. Given that GABAergic inhibition shrinks the size of tactile receptive fields in SI [132], increased intracortical inhibition could account simultaneously for this visual enhancement of touch and visual analgesia. Indeed, seeing the body does in fact increase intracortical inhibition in SI compared to seeing an object [131], at least in studies using non-noxious tactile stimuli.

Thus, we suggest that vision of the body generates analgesia by increasing intracortical inhibition in SI. This may transiently modulate somatosensory representations, producing sharper, less-overlapping somatotopic maps. Several aspects of chronic pain are consistent with this interpretation. First, chronic pain is commonly associated with reduced tactile sensitivity on the painful body part [70,71,133] and disorganisation of somatotopic maps in SI [71,134–138]. Further, the magnitude of somatosensory disorganisation is a strong predictor of pain severity [134,135,139]. Conversely, tactile discrimination training, which should promote organisation of somatosensory maps, is an effective treatment for chronic pain, presumably by sharpening somatotopic maps of the body in primary somatosensory cortex [140,141]. Intriguingly, the effectiveness of tactile discrimination training increases when CRPS patients view the body part being trained [141]. These results indicate that reduced organization of somatosensory maps, which we may call *somatosensory blurring*, plays an important causal role in the experience of pain. Conversely, promoting organization of SI, what we call *somatosensory sharpening*, produces analgesia for both chronic and acute pain.

Influence of Nociceptive Afferent Input on Body Representation

The finding of visual analgesia from seeing the body reveals an important way in which higher-order information about the body can modulate pain in a top-down fashion. Other evidence has revealed evidence for the converse relation as well, showing that nociceptive afferent signals play an important regulatory role in maintaining the representation of the body. It has long been known that anesthesia, whether of individual parts or of the entire body, does not produce the feeling that the body has vanished, but rather produces phantom sensations of the body [142].

These results demonstrate that our conscious experience of our body is not driven by immediate sensory inputs, but rather by a central *body image* [113]. The phantom experiences, however, do not exactly match the normal body image, suggesting that the body image depends to some extent on continuous afferent input. Phantom sensations following spinal cord injury are frequently characterized by increases in the experienced size of the body [143–145].

Similar results have been found following acute anesthesia. For example, local anesthesia of the thumb produces an increase in the perceived size of the thumb [146]. This phenomenon is familiar to people who have had anaesthetic injections at the dentist: the entire mouth feels swollen and enormous [147]. Similar results have also been reported

following anesthesia of the brachial plexus, generating the experience of the entire arm being swollen [148].

Intuitively, these results seem surprising: reducing inputs from a body part might be expected to *reduce*, rather than increase, its perceived size. What accounts for the increase in perceived size? Because anesthesia affects different types of afferent fibres at different rates, the time-course of illusions of perceived body size can be matched with changes in function of specific fibre classes. Using this method, Paqueron and colleagues [26,148,149] found that changes in perceived size were correlated with reduced sensitivity to pin-prick and thermal sensations, suggesting that they are related to the offset of signals from small-diameter Aδ and C fibres.

These results are particularly intriguing in light of findings that C fibres provide continuous inhibition to primary somatosensory cortex [150]. Thus, deafferentation may reduce inhibition in SI, producing increased overlap between representations of adjacent skin surfaces (somatosensory blurring). This may generate perceived swelling by increasing the total number of neurons representing the affected body part. This disinhibition may also have an important role in the generation of phantom limb pain following deafferentation [7].

Altered Body Representation in Chronic Pain

Chronic pain is impossible to ignore, and commonly dominates the patient's mental life. Ironically, however, there is also evidence that chronic pain is associated with 'neglect-like' symptoms [151–153] or 'body perception disturbance' [154,155], in which the affected limb is misperceived. These symptoms reflect a constellation of symptoms with intriguing similarities to disorders of body representation that follow right parietal lobe damage [156]. Some patients report that their affected limb feels "like dead weight" and that focused attention is required to move the limb, while others report feeling that the painful limb feels "foreign" or "strange", as if it were not part of the patient's body [152–154].

In one large survey of CRPS patients, 84% of patients reported at least one such neglect-like symptom [152]. Such reports are intriguingly similar to previous reports of 'asomatagnosia' following parietal lobe damage, in which patients report feeling like the contralateral side of their body is absent [156]. In some cases, these feelings of foreignness result in hostility towards the limb ('misoplegia') [154,157] and even desire to have the limb amputated [154,158]. In other cases, there is clear evidence for sensory abnormalities related to the affected body part, including unawareness of limb position [155,157], referral of sensations to adjacent body parts [139,159], and displacement of the perceived body midline towards the affected side [160].

In addition to the neglect-like symptoms caused by chronic pain, visual hemi-neglect itself also alters pain perception. In particular, Liu and colleagues [161] observed a mislocalization of painful stimuli to the ipsilesional size of the body, and a misidentification of stimulus modality in neglect patients.

Several forms of chronic pain have also been found to be associated with distortions of the perceived size or shape of the affected body part, including CRPS [154,162,163], chronic back pain [133], and chronic pelvic pain [164]. In general, the affected body part is perceived as being larger than it really is. This pattern is intriguingly similar to the pattern observed following deafferentation (see above), and is consistent with the interpretation that blurred somatosensory maps play a critical role in generating chronic pain.

Such results suggest an intimate relation between chronic limb pain and distortions of body representation. In most cases, however, the causal direction of this relation is unclear. Intriguingly, however, the patient described by Bultitude and Rafal [157] developed CRPS following fracture of her right hand and reported feelings of foreignness and unawareness of limb position while her limb was immobilized, but *before* she experienced CRPS pain. This suggests that distorted body representation may be a cause, rather than a consequence, of chronic limb pain. Similarly, Moseley and colleagues [120] showed that visual magnification of the affected body part increased CRPS pain, while visual size reduction attenuated it. This mirrors the bias to perceive the affected limb as bigger than it actually is [162,163] and demonstrates a causal effect of body representation on pain.

Implications for Chronic Pain

This review has focused largely on experimental studies of acute pain. Nevertheless, the knowledge we have summarized has potential clinical implications. Chronic pain is defined, according to duration and appropriateness, as pain without apparent biological value that has persisted beyond the normal tissue healing time [1]. It is a common and severe consequence of injuries to either peripheral tissues or to the nervous system itself. For a comprehensive introduction to chronic pain syndromes, the reader is directed to the several excellent reviews and textbook chapters [7,165,166]. The findings discussed in this review suggest that interactions of pain with other somatosensory submodalities, and with visual information about the body, offer the possibility to modulate chronic pain. Mirror-box therapies were recently advocated as a possible therapy for chronic pain, including phantom limb pain and CRPS [167]. However, the efficacy of these therapies has been disputed [168].

Our review of the neural mechanisms that integrate pain and body representation has several implications for the search for multisensory therapies. First, this search should not be abandoned as hopeless, since there is clear evidence for neurophysiological mechanisms for multisensory interactions involving the nociceptive system, on which such therapies should rely. Second, there is a need for future research to use multiple sensory modalities, and not only vision, as potential interactors with pain. Third, multisensory interactions involving nociception reveal a strong principle of spatial organization. Since chronic pain is often very specifically localized to a single body part, and since reorganization of spatially-mapped cortical areas appears relevant to chronic pain, future research might usefully investigate how to harness the spatial organization of body-pain interactions in order to modulate chronic pain.

Conclusion

In conclusion, we have argued pain is not only a distinct class of sensation, but also a distinct form of information about one's own body. Perceptual and motor responses to painful stimuli suggest that the brain codes nociceptive information according to a spatial organizing principle that mixes representations of the body surface with representations of the position of body parts in external space. Interactions between pain and other somatosensory modalities suggest

that pain contributes to the multisensory cortical representations that underlie the sense of one's own body and of peripersonal space. The precise significance of such multisensory representations of the body remains unclear, though several lines of cognitive and neuroimaging research suggest that they may provide the neural basis of both coordinated spatial interactions with the nearby environment, and of self-consciousness. Our review shows that the physiological systems underlying pain are strongly integrated in these representations.

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