OPINION

How do you feel? Interoception: the sense of the physiological condition of the body

A. D. Craig

As humans, we perceive feelings from our bodies that relate our state of well-being, our energy and stress levels, our mood and disposition. How do we have these feelings? What neural processes do they represent? Recent functional anatomical work has detailed an afferent neural system in primates and in humans that represents all aspects of the physiological condition of the physical body. This system constitutes a representation of 'the material me', and might provide a foundation for subjective feelings, emotion and self-awareness.

The feelings we perceive from our bodies include temperature, pain, itch, tickle, sensual touch, muscular and visceral sensations, vasomotor flush, hunger, thirst, AIR HUNGER and others related to the body's state. Early German physiologists regarded such general bodily feelings as *Gemeingefühl*, or 'common sensation', and distinguished them from the five senses[1]. Sir Charles Sherrington conceptualized a sense of 'the material me' by considering that all of these feelings are related and form a foundation for the sense of one's physical self[2]. William James presented similar natural philosophical arguments and regarded the feelings from our bodies as the basis for self-awareness and emotion[3]. However, Sherrington later codified the senses into teloreceptive (vision and hearing), proprioceptive (limb position), exteroceptive (touch), chemoreceptive (smell and taste) and interoceptive (visceral) modalities, and he categorized temperature and pain as aspects of touch[4].

Recent findings on the functional anatomy of the lamina I spinothalamocortical system indicate that interoception should be redefined as the sense of the physiological condition of the entire body, not just the viscera[5–7]. This system is a homeostatic afferent pathway that conveys signals from small-diameter primary afferents that represent the physiological status of all tissues of the body. It projects first to autonomic and homeostatic centres in the spinal cord and brainstem, thereby providing the long-missing afferent complement of the efferent autonomic nervous system. Together with afferent activity that is relayed by the nucleus of the solitary tract (NTS), it generates a direct thalamocortical representation of the state of the body in primates that is crucial for temperature, pain, itch and other somatic feelings. This anatomical organization shows that these feelings are highly resolved, sensory aspects of ongoing homeostasis that represent the physiological condition of the body itself — a distinct shift from the concept that pain and temperature are aspects of touch. Converging evidence from functional imaging studies substantiate this interoceptive cortical image and indicate that its re-representation in the anterior insular cortex of the non-dominant (right) hemisphere, possibly uniquely in humans, constitutes a basis for the subjective evaluation of one's condition, that is, 'how you feel'.

Background

The view represented in most textbooks regards pain and temperature as distinct, discriminative, cutaneous sensations that are relayed to somatosensory areas of the cortex by the thalamic ventrobasal complex[8,9] (FIG. 1). Visceral sensations are assigned to a system that relays vagal, glossopharyngeal, facial and spinal afferent activity by way of the brainstem parabrachial nucleus to the same ventrobasal complex, but then to the insular cortex — a fact that is used to explain why such sensations are less distinct[10,11].

However, these concepts could not explain several important discrepancies. First, the involvement of the somatosensory cortex is challenged by the fact that pain and temperature sensations remain after cortical lesions of the postcentral gyrus. For this reason, Head and Holmes[12] assigned awareness of pain sensation to the posterolateral thalamus and prescribed a modulatory role for the cortex. Second, the association of pain with touch implies the existence of convergent, modifiable pain-and-touch cells (considered to be the so-called 'wide dynamic range' cells of the deep dorsal horn[9,13,14]), despite the obvious inability of such modality-ambiguous cells to engender the distinct sensations elicited by different stimuli (for example, sharp versus burning pain). Third, although there is a clear need for an afferent pathway to elicit efferent autonomic adjustments to somatic events that produce feelings from the body (for example, for the ongoing homeostatic process of thermoregulation[15]), the concept of a 'sympathetic afferent' system has often been dismissed[10,11].

The prevailing views also stumbled on the fundamental fact, recognized long ago[16], that, in the central nervous system, pain, temperature and itch sensations are distinguished from touch by their association with the spinothalamic projection, which ascends in the contralateral spinal cord, rather than with the dorsal column/medial lemniscal system in the ipsilateral spinal cord. Because of this arrangement, spinal hemisection produces contralateral loss of pain and temperature

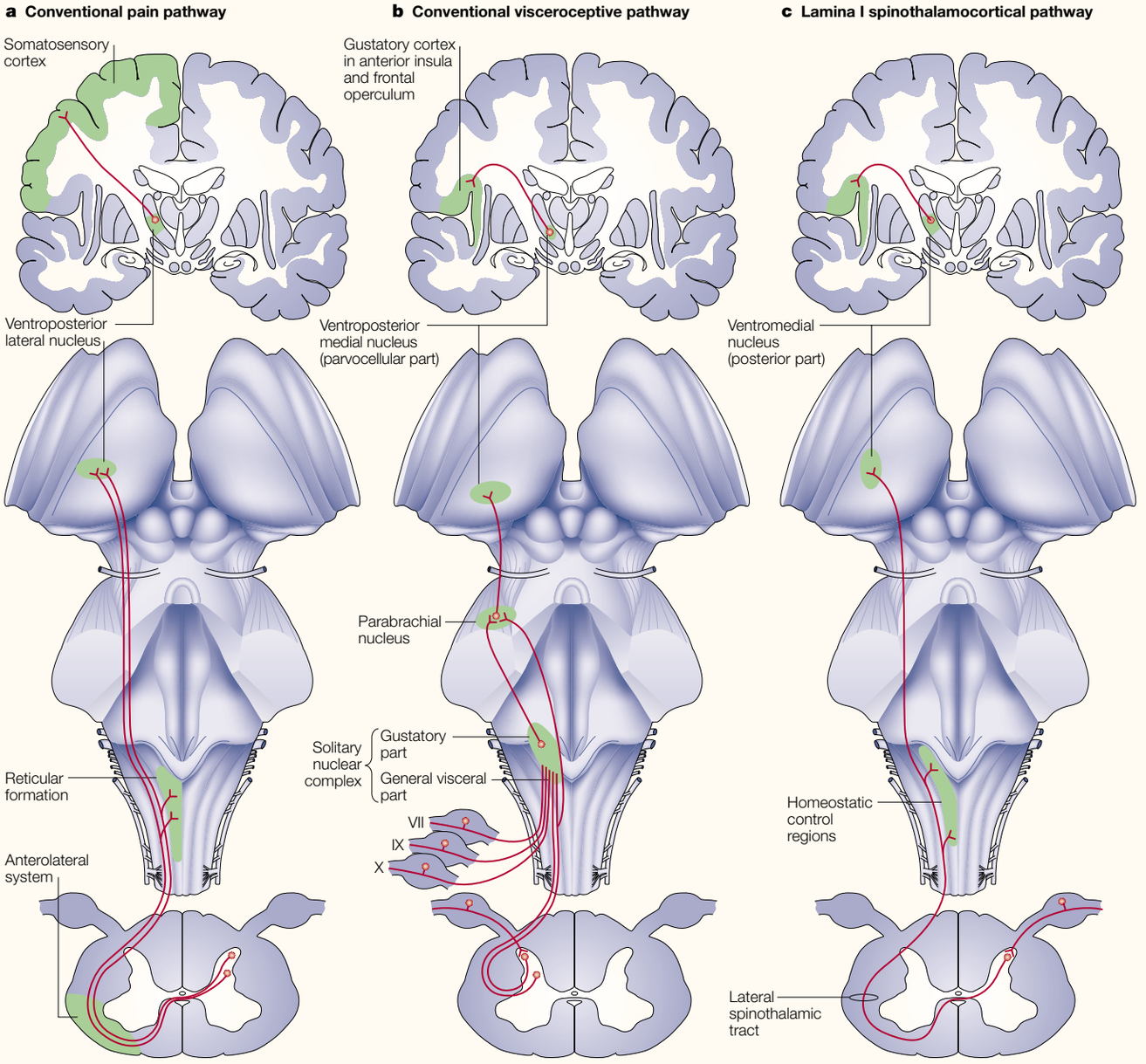


Figure 1 | **Pain, visceroceptive and spinothalamocortical pathways.** Comparison of organizational charts of **a** | the conventional view of pain pathways, **b** | the conventional view of visceroceptive pathways and **c** | the lamina I spinothalamocortical pathway.

sensations, and ipsilateral loss of fine-touch perception (the Brown–Sequard syndrome). Phylogenetic arguments that defined so-called 'palaeo-' and 'neo-' spinothalamic systems attempted to explain how pain and temperature were part of the touch system at the thalamocortical level, although separate at the spinal level[17,18]. However, the fundamental commonality of pain, temperature and other bodily sensations as interoceptive, rather than exteroceptive, remained unrecognized.

A key feature that distinguishes pain, temperature and other bodily feelings from touch is their inherent association with emotion (but see the discussion below on sensual touch). These feelings all have not only a sensory, but also an affective, motivational aspect. The emotional aspect of thermal sensation, in particular, is easily under-appreciated; we typically project temperatures onto the object we are touching or onto our environment, as Aristotle did. However, temperature is ultimately a physiological condition of the tissue itself (and likewise for all bodily feelings), and it generates an inseparable affect (pleasantness or unpleasantness) — a feeling — that signals its homeostatic role. Accordingly, this feeling is directly dependent on the body's needs[19,20]. For example, compare the pleasant feeling of cool water when your body is overheated with the gnawing discomfort generated by the very same cool stimulus when you are 'chilled to the bone'. Thermoregulation is a primal evolutionary requirement for all animals, particularly homeothermic mammals, and the affective aspects of such feelings correspond to the motivations that are essential for behavioural thermoregulation and homeostasis — that is, survival[21,22]. Thermoreception is therefore

representative, because all of the feelings from the body are directly related to homeostatic needs and associated with behavioural motivations that are crucial for the maintenance of body integrity, and their neural representation reflects this homeostatic primacy.

The ascending neural activity that represents temperature and other physiological conditions of the body is conveyed by the lamina I spinothalamocortical pathway (FIG. 1). The physiological and anatomical characteristics of this system will first be reviewed, and then the functional imaging and clinical evidence that documents the primary interoceptive cortex will be summarized. Finally, the cortical re-representations of interoceptive state that provide the basis for subjective awareness of the feelings from the body will be described and related to concepts of self-awareness and consciousness.

The functional anatomy of lamina I

Lamina I, the most superficial layer of the spinal (and trigeminal) dorsal horn, is the only neural region that receives monosynaptic input from small-diameter (Aδ and C) primary afferent fibres, which innervate essentially all tissues of the body[6]. The adjacent lamina II (substantia gelatinosa) was once described as the pain-processing region of the dorsal horn, but it contains only local interneurons in cat and monkey, and it essentially receives C-fibres only from skin. (In rodents, lamina II is less distinct from lamina I.) Lamina I is the source of output from the superficial dorsal horn, contributing half of the spinal input to the brainstem and thalamus. It is usually associated with 'pain and temperature' and, indeed, its projections contain LABELLED LINES that specifically subserve these sensations. However, the evidence indicates that these are simply particular aspects of interoception and that lamina I neurons fundamentally represent many aspects of the physiological condition of the tissues of the body.

The association of small-diameter afferents and lamina I neurons begins with their development, which is temporally coordinated and distinguished from the large-diameter exteroceptive and proprioceptive afferents that project to the deep dorsal horn; this developmental differentiation seems to reflect a simple physiological distinction between the inside and outside of the body. Whereas the large-diameter fibres originate from the first wave of large (A) dorsal root ganglion cells, the small-diameter afferents originate from small (B) cells and enter the spinal cord in a second wave, subsequent to the larger fibres. Their arrival in the dorsal horn is genetically coordinated to coincide with the arrival of lamina I neurons. The lamina I neurons, which arise from the progenitors of autonomic interneurons in the lateral horn, migrate to their superficial dorsal position during a ventromedial rotation of the entire dorsal horn, which occurs simultaneously with the arrival of the small-diameter afferents[23]. A common transcription factor (DRG11) is activated in the B cells and lamina I neurons at this time[24]. This rotation places the small-diameter afferent fibres that enter by the lateral division of the dorsal root in contact with lamina I neurons. This rotation concurrently results in the characteristic recurrent trajectory of the large-diameter fibres, which do not connect with lamina I neurons[25]. This course of development supports the view that the small-diameter afferents and lamina I constitute a cohesive homeostatic afferent system.

The Aδ- and C-type primary afferent fibres that are relayed by lamina I relate homeostatic information — that is, much more than simply 'pain and temperature' sensations — from all tissues. These fibres convey slow activity that is sensitive to changes in a wide variety of physiological conditions — not only temperature and mechanical stress, but also local metabolism (acidic pH, hypoxia, hypercapnia, hypoglycaemia, hypo-osmolarity and lactic acid), cell rupture (ATP and glutamate), cutaneous parasite penetration (histamine), mast cell activation (serotonin, bradykinin and eicosanoids), and immune and hormonal activity (cytokines and somatostatin)[6,7,26–30]. This perspective emphasizes that the category 'nociceptors', although heuristically of enormous value, is actually a theoretical simplification, because the empirical mechanical, thermal and polymodal thresholds of small-diameter afferents extend broadly across the 'pain' threshold in all tissues, as expressed clearly by many investigators[31–34]. Microneurographic data indicate that only the summated activation of 'C-nociceptors' causes a conscious perception of 'pain' in humans[35], and C-fibres often have slow ongoing discharge without provocation, which is not perceived[34,36,37] and is likely to be related to current tissue metabolic status. In addition, many cutaneous C-fibres are selectively and exquisitely sensitive to slow, weak mechanical stimuli that evoke sensual ('limbic') touch[38], as are neurons in lamina I and in the inner substantia gelatinosa[39].

The ascending projections of lamina I neurons, which have been detailed in cat and monkey, unambiguously indicate their role in homeostasis[6,40,41] (FIGS 1 and 2). First, they project strongly to the sympathetic cell columns of the thoracolumbar spinal cord. Next, they project to the main homeostatic integration sites in the brainstem. The latter include regions that also receive vagal and glossopharyngeal afferent activity (by way of the solitary nucleus) and are heavily interconnected with the hypothalamus and amygdala — that is, the ventrolateral medulla, catecholaminergic cell groups A1, A2 and A5–A7, the parabrachial nucleus and the periaqueductal grey. Lamina I terminations in the medulla coincide precisely with the developmental border between the

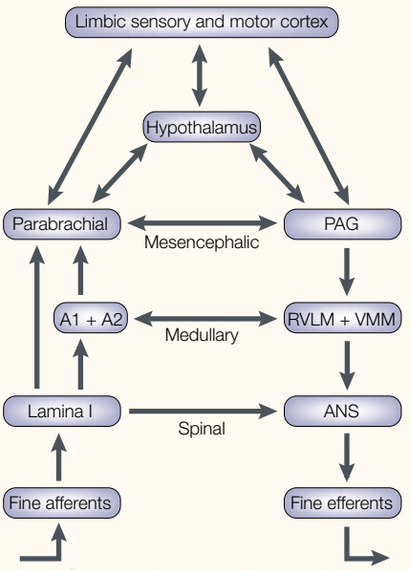
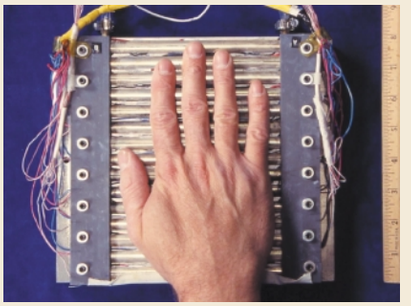
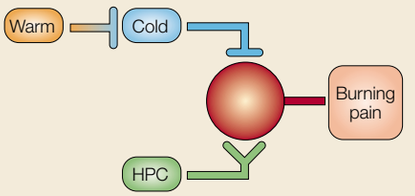


Figure 2 | **Hierarchical organization of neural homeostasis involving the sympathetic nervous system.** Small-diameter afferent fibres that report the physiological condition of all tissues of the body terminate in lamina I of the spinal and trigeminal dorsal horns. The ascending projections of lamina I neurons provide the bases for somato-autonomic reflex arcs at the spinal, medullary and mesencephalic levels. At the spinal level, lamina I projects strongly to the sympathetic regions in the intermediomedial and intermediolateral cell columns of the thoracolumbar cord, where the sympathetic preganglionic cells of the autonomic nervous system (ANS) originate. In the medulla, lamina I neurons project to the A1 and A2 catecholaminergic cell groups and to other sites (including the rostral ventrolateral medulla, RVLM), which are interconnected with the pre-sympathetic neurons that project to spinal levels. The A2 cell group (that is, the nucleus of the solitary tract) also receives direct parasympathetic (vagal and glossopharyngeal) afferent input (not shown), and A1 projects to the hypothalamus. In the pons and mesencephalon, lamina I neurons project to the parabrachial nucleus, the main brainstem homeostatic integration site, and to the periaqueductal grey (PAG), the main homeostatic brainstem motor site. The hypothalamus (the main autonomic control centre) and the limbic cortical regions project to all of these sites in the brainstem, and to lamina I and the sympathetic preganglionic regions in the spinal cord. VMM, ventromedial medulla.

Box 1 | **The thermal-grill illusion of pain**





Thunberg's (1896) thermal grill evokes a burning, ice-like pain sensation with interlaced innocuous warm (40 °C) and cool (20 °C) bars. A similar, albeit stronger, sensation is elicited by pouring warm water on feet that are numb with cold (an unmistakable signal of thermoregulatory distress), and only burning pain is evoked by a cool stimulus (<24 °C) when A-fibre conduction (and normal cool sensation) is blocked by pressure on a peripheral nerve. These demonstrations reveal two basic phenomena: the increasing activation of the polymodal C-nociceptive sensory channel by cold below a threshold of ~24 °C (the normal thermoneutral ambient temperature), and the central inhibition of that activity by innocuous thermosensory activity ('cold inhibits pain').

The burning pain sensation caused by polymodal C-nociceptors (HPC), which are sensitive to noxious heat and pinch, as well as to cold, is normally masked centrally by the activity of the specific cutaneous Aδ-fibre thermoreceptors that are responsible for the sensation of cooling. When the activity of cooling receptors is reduced, the polymodal nociceptive activity that is evoked by cooling is disinhibited centrally and causes a burning sensation at cool (<24 °C) temperatures that is normally felt only at noxious cold (<15 °C) temperatures.

The thermal-grill illusion can be explained physiologically by an unmasking of the cold-evoked activity of polymodal nociceptive lamina I spinothalamic neurons (which are selectively activated by polymodal C-nociceptors) due to the reduction of the normal cold-evoked activity of thermoreceptive lamina I spinothalamic neurons (which are selectively activated by Aδ-type cooling thermoreceptors) by spatial summation of the simultaneous warm stimuli in the thermoreceptive but not the nociceptive neurons[62]. The grill effectively produces a relative balance of polymodal and thermosensory activity similar to that caused by a noxious cold stimulus of ~10 °C; the equivalence of these sensations has been verified psychophysically. Reduction of activity in the thermoreceptive sensory channel disinhibits or unmasks the polymodal nociceptive channel at thalamocortical levels, producing a burning pain sensation.

Functional imaging has confirmed that the thermal grill produces a pattern of activity in the cortex that is identical to the activation produced by noxious cold[63]. The cortical activation unmasked by the grill is in the anterior cingulate cortex (ACC), indicating that ACC activation is selectively associated with the perception of thermal pain — that is, the affect that signals thermoregulatory distress. So, the thermosensory activity in the lamina I spinothalamocortical pathway to interoceptive cortex unmasks activity in the medial lamina I pathway, which activates the ACC and is associated with burning pain. This indicates that the medial thalamic lamina I spinothalamic tract projection to the mediodorsal thalamic nucleus (ventral caudal part, MDvc) might be the crucial site for the inhibition of thermal pain by cold; this suggestion is supported by preliminary physiological recordings from the MDvc in our laboratory.

alar and basal plates that defines the classic 'general visceral afferent' integration region[42], and throughout the brainstem they co-localize with the catecholaminergic cell columns that identify homeostatic regions. These spinal and bulbar lamina I projections substantialize (provide the anatomical substrate for) the somato-autonomic reflexes that are activated by small-diameter afferents (including viscerosensitive activity) and are crucial for cardiorespiratory and other homeostatic functions[43,44]. Importantly, these reflex pathways are not simply emergency mechanisms; rather, they provide continuous homeostatic feedback. For example, respiration is linearly modulated by graded changes in innocuous thermosensory activity[45]. Completing this anatomical circuitry, lamina I receives descending modulation directly from brainstem pre-autonomic sources (A5, A7 and raphe nuclei). Most strikingly, the only spinal regions that receive descending controls directly from the hypothalamic paraventricular nucleus — the main diencephalic autonomic control centre — are the autonomic motor nuclei and lamina I[46].

Lamina I neurons relate many aspects of the ongoing physiological status of the tissues of the body. In cat and monkey, they comprise several distinct, modality-selective classes that receive input from particular subsets of small-diameter fibres. These classes of neurons serve as labelled lines, because they differ morphologically, physiologically and biochemically, and their activity corresponds to distinct sensations[47,48]. Primarily on the basis of cutaneous stimulation (and the heuristic concept of nociception), we now recognize two classes of neurons that signal sharp pain (FIRST PAIN) and burning pain (SECOND PAIN) that selectively receive inputs from Aδ-nociceptors and polymodal C-nociceptors, respectively[49,50]. In addition, there are two types of thermoreceptive lamina I cell that respond selectively to cooling or to warming, distinct types of chemoreceptive cell that respond selectively to histamine or to noxious chemicals, and other classes that respond selectively to muscle or joint afferents or to mechanical 'slow brush' (tickle)[39,51–54]. A particularly convincing demonstration of the selectivity inherent in this pathway is provided by the histamine-responsive cells that we recently identified, which constitute a specific pathway for the sensation of itch[55]. Further types remain to be documented more clearly. For example, although most viscerosensitive lamina I cells reported so far have convergent cutaneous input[54,56,57], such cells might have been sensitized by the requisite surgical preparation and repeated visceral search stimulation, and distinct types of viscerosensitive cell probably exist that even distinguish renal artery from renal vein occlusion by responding selectively to renal osmoreceptors or mechanoreceptors[58], similar to the selectively metaboreceptive muscle-responsive lamina I neurons that we recently identified (see below)[59]. In stark contrast to these neurons, the cells in the deep dorsal horn provide a modality-ambiguous integration of all afferent inputs, including mechanoreceptive, proprioceptive and nociceptive activity[9,60,61].

The thermoreceptive lamina I cells that are sensitive to cooling respond predominantly to Aδ-fibre input and have ongoing discharge at normal skin temperature that is inhibited by warming. They uniquely evince a linearly increasing response to skin temperatures below a neutral skin temperature (~34 °C) that corresponds directly with human psychophysics[48]. Their activity reaches a plateau at the cold temperatures that we perceive as noxious (<15 °C); at these temperatures, the polymodal nociceptive cells that signal burning (second) pain are increasingly active. Analysis of the thermal-grill illusion of pain (BOX 1) indicates that the perception of thermal distress and cold pain depends on the comparison of these two sensory channels in the forebrain[62,63], as well as on core temperature[20]. Notably, the

polymodal nociceptive channel responds to cold with accelerating activity below ~24 °C — corresponding to our increasing thermoregulatory distress below a thermoneutral ambient temperature — and, when Aδ-type thermoreceptive afferent activity is reduced by a nerve block or by the thermal grill, the activity in this channel elicits a burning-pain sensation at such temperatures[48,62,64]. This emphasizes that pain is not a binary (yes or no) modality, and compels the conceptual shift of viewing the role of polymodal C-nociceptors and the lamina I neurons that convey their activity as a homeostatic afferent pathway rather than simply a 'nociceptive' pathway.

To directly address the role of lamina I in homeostasis, we recently examined the responses of lamina I neurons to muscle contraction. We identified a class of lamina I spinobulbar neurons that respond selectively during and after muscle contraction. These neurons provide a substrate for the EXERCISE PRESSOR REFLEX[59]. Some of the muscle Aδ- and C-fibres that are represented by these lamina I cells are sensitive to contraction; others are sensitive to lactic acid and other metabolites released during muscular exercise, and can be viewed as metaboreceptors (or ERGORECEPTORS) that continuously drive a variety of regional and whole-body homeostatic adjustments to muscular work[36,65–67]. It is important to recognize that large increases in such activity can cause the familiar aching or burning sensation from muscles, and synchronous activation causes a painful cramping sensation[68], but the activity elicited continuously by muscle contraction normally produces homeostatic adjustments without the perception of a behaviourally motivating signal. This class of neurons clearly confirms the role of lamina I in ongoing homeostasis, and substantiates the concept that it relates the current physiological condition of all the tissues of the body.

Lamina I spinothalamocortical pathway

Anterolateral cordotomy in humans interrupts contralateral temperature, pain, itch, sensual touch and visceral sensations, if made at the location of ascending lamina I axons in the lateral spinothalamic tract[6,69]. In primates, lamina I spinothalamic neurons project to a dedicated thalamocortical relay nucleus in the posterolateral thalamus — the posterior part of the ventromedial nucleus, or VMpo[70] (FIGS 1 and 3). The VMpo is small in the macaque monkey thalamus, and it is only primordially represented in sub-primates, but it is proportionately very large in the human thalamus[71]. It has appropriate anatomical characteristics for a thalamic relay nucleus: dense clusters of large, glutamatergic lamina I boutons that are organized topographically (in the rostrocaudal direction) and associated with TRIADIC ARRANGEMENTS of GABA (γ-aminobutyric acid)-containing presynaptic dendrites and proximal relay cell dendrites in cytoarchitectonically distinguishable cell nests[70,72]. The VMpo is contiguous rostrally with the basal part of the ventromedial nucleus, or VMb (which, for historical reasons, is denoted by some as the parvicellular part of the ventroposterior medial nucleus, or VPMpc, even though it does not project to the somatosensory cortex as the remainder of the VPM does) and, in primates, VMb receives a direct (bilateral) input from the nucleus of the solitary tract, which conveys vagal and glossopharyngeal (general visceral and gustatory) afferent activity[73]. Therefore, these two thalamic nuclei together represent all homeostatic afferent inflow (both sympathetic and parasympathetic) from the body, and they form a separate, rostrocaudally organized column that is orthogonal to the mediolateral alignment of the exteroceptive and proprioceptive representations in the ventroposterior nuclei, to which they are connected at the representation of the mouth. The direct lamina I pathway to VMpo and the direct pathway from the nucleus of the solitary tract to VMb are distinguishable only in primates; essentially, homeostatic afferent input in sub-primates reaches the forebrain after integration in the brainstem parabrachial nucleus[10] and by direct spinohypothalamic projections (in rats)[74].

Nociceptive and thermoreceptive neurons with properties similar to lamina I neurons have been identified in VMpo in macaque and owl monkeys[70,75], and such neurons have also been recorded in the region of VMpo in awake humans[76,77]. These different modalities are segregated within VMpo. Significantly, microstimulation in this region of the thalamus in awake humans elicits discrete pain or cooling or visceral sensations[77–80]. Anatomical tracing in monkeys indicates that VMpo and VMb project in a rostrocaudally topographic fashion to a cytoarchitectonically distinct field in the fundus of the superior limiting sulcus at the dorsal margin of insular cortex, with the VMb projection field extending rostrally from the VMpo projection to include the previously recognized gustatory cortex[6,81,82]. A smaller, ancillary VMpo projection terminates in area 3a in the fundus of the central sulcus. These anatomical and functional findings directly contradict the conventional view of pain processing and the view of some investigators that nociceptive activity simply passes through the posterior thalamus to VPM and VPL and thence to the somatosensory cortex[9].

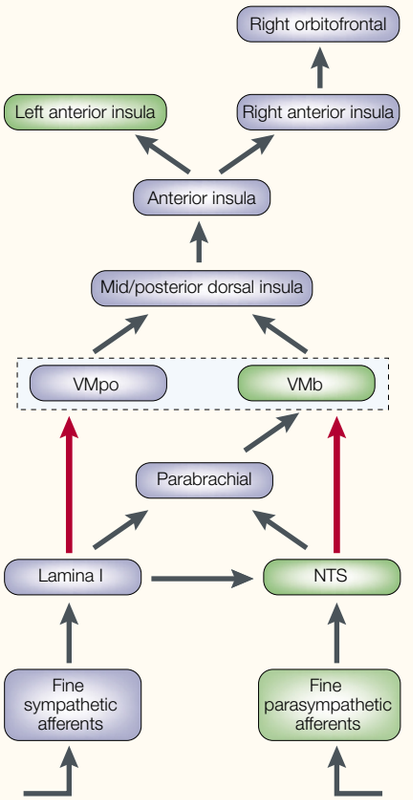


Figure 3 | **The organizational chart for interoception.** Small-diameter afferents that innervate tissues in parallel with sympathetic efferents ('sympathetic afferents') provide input to lamina I; small-diameter afferents that innervate tissues in parallel with parasympathetic efferents ('parasympathetic afferents') provide input to the nucleus of the solitary tract (NTS). In mammals, such activity is integrated in the parabrachial nucleus, which projects to insular cortex by way of the ventromedial thalamic nucleus (VMb, also known as VPMpc). In primates, however, a direct projection from lamina I to the ventromedial nucleus (VMpo), and a direct projection from the NTS to the VMb, provide a rostrocaudally contiguous column that represents all contralateral homeostatic afferent input and projects topographically to the mid/posterior dorsal insula. In humans, this cortical image is re-represented in the anterior insula on the same side of the brain. The parasympathetic activity is then re-represented in the left (dominant) hemisphere, whereas the sympathetic activity is re-represented in the right (non-dominant) hemisphere. These re-representations provide the foundation for a subjective evaluation of interoceptive state, which is forwarded to the orbitofrontal cortex, where hedonic valence is represented in mammals.

Functional imaging with PET (positron emission tomography), SPECT (single-photon emission computed tomography) and fMRI (functional magnetic resonance imaging) verify that the anatomically identified

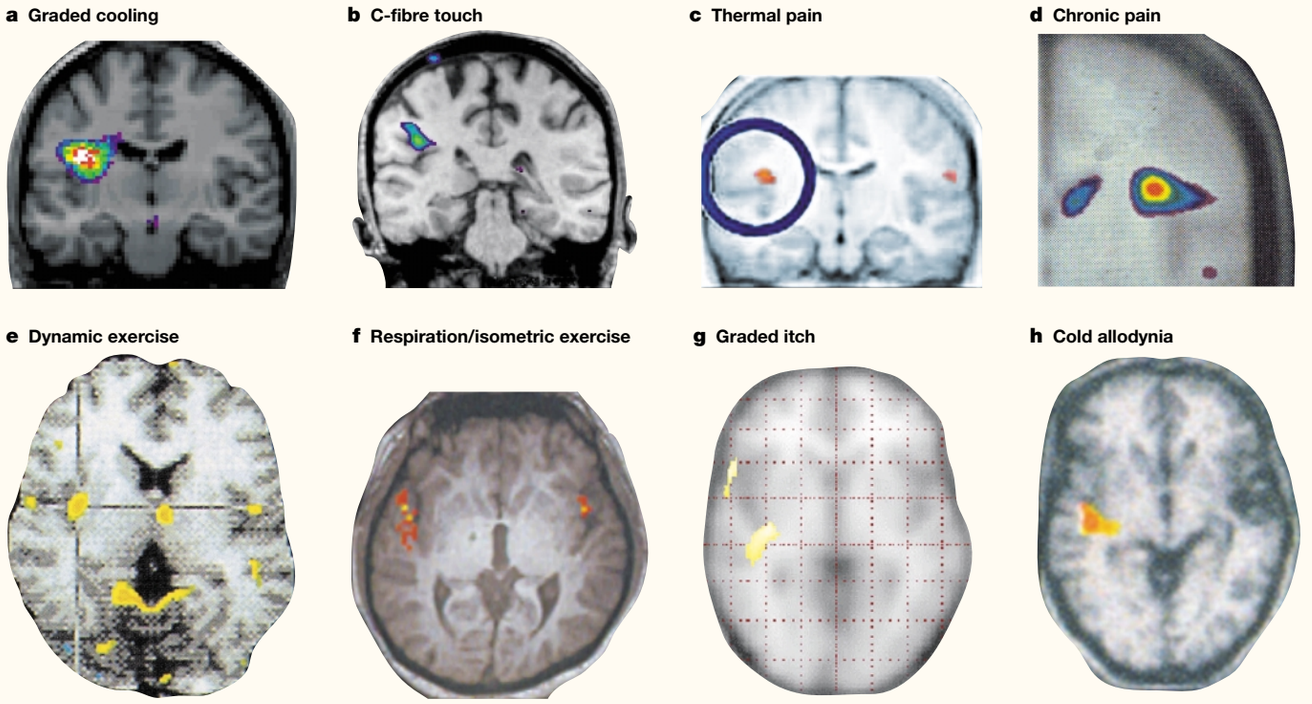


Figure 4 | **Activation of the interoceptive cortex in the dorsal posterior insula by various modalities. a** | Graded cooling (reproduced, with permission, from REF. 5 © 2000 Macmillan Magazines Ltd). **b** | Sensual (limbic) touch evoked by slow brushing in a polyneuropathy patient with only C-mechanoreceptor activation (reproduced, with permission, from REF. 101 © 2002 Macmillan Magazines Ltd). **c** | Thermal pain (reproduced, with permission, from REF. 91 © 2002 Elsevier Science). **d** | Chronic pain (reproduced, with permission, from REF. 92 © 2001 International Association for the Study of Pain). **e** | Dynamic exercise on a bicycle (reproduced, with permission, from REF. 96 © 1999 The American Physiological Society). **f** | Forced respiration and isometric exercise with a hand grip (reproduced, with permission, from REF. 95 © 1999 John Wiley & Sons). **g** | Graded itch elicited by cutaneous histamine injection (reproduced, with permission, from REF. 94 © 2001 International Association for the Study of Pain). **h** | Cold allodynia (reproduced, with permission, from REF. 93 © 2000 International Association for the Study of Pain).

VMpo/VMb projection field in the dorsal insular cortex is activated by temperature, pain and numerous interoceptive modalities that cause feelings from the body, consistent with the functional anatomical data on lamina I (FIG. 4). This site is distinct from the parietal somatosensory cortices, supporting the idea of a neural distinction of interoception from exteroception. Our PET study using graded innocuous cooling of the hand showed correlated activity only at this site in the fundus of the superior limiting sulcus of the posterior insula[5]. This site coincides with the location of cortical lesions that produce thermanaesthesia and hypalgesia[83,84], and it verifies that the terminus of the lamina I spinothalamocortical pathway is the same in humans as in monkeys. In human atlases, this site has been included with the parietal operculum as the second somatosensory region (S2), on the basis of comparative anatomical tracing work that was carried out before the recognition of VMpo[85]. However, this site is distinct from S2. The S2 has a topography that is aligned from lateral to medial (face to foot[86]), which is orthogonal to the rostrocaudal topography in the interoceptive VMpo cortical field. So, tactile stimulation of the hand activates a portion of S2 close to the lip of the lateral sulcus, more than 16 mm lateral to the site in the dorsal posterior insula that is activated by cooling the hand.

This same region in the dorsal posterior insula (albeit slightly more rostrally) shows (graded) activity in every imaging study that uses noxious heat applied to the hand[87–91]. It shows ongoing activity in chronic pain patients[92], as well as evoked activity in NEUROPATHIC PAIN patients, in which pain can be caused by normally innocuous stimuli[93]. (In anaesthetized monkeys, noxious cold stimuli produce fMRI activation at precisely the sites identified in our anatomical tracing studies[6].) Furthermore, this same dorsal posterior insular site shows graded activity that is correlated with itch sensation in humans[94]. This interoceptive site is activated by both isometric and dynamic exercise[95,96], like the lamina I neurons that respond selectively during and after muscle contraction[59]. It is activated by a range of modalities associated with visceral sensations, such as the Valsalva manoeuvre, manipulations of blood pressure (maximal inspiration; lactate or cholecystokinin injection), thirst (hypertonic saline injection), hunger and air hunger[95,97–99]. Consistent with the anatomical tracing studies, gustatory stimuli activate the dorsal insular cortex more rostrally[100]. Activation of this interoceptive cortex was also observed using light, slow brushing in a patient with polyneuropathy who has only peripheral nerve C-fibre conduction, consistent with the essential role of lamina I and the lateral spinothalamic tract for sensual (limbic) touch[101,102].

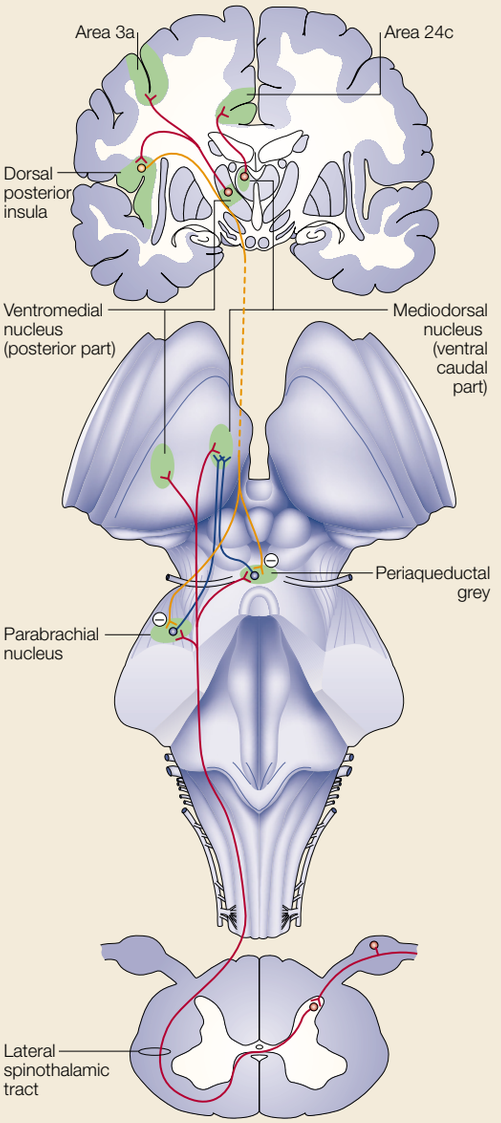
So, the evidence indicates that, in primates, the dorsal insular cortex contains a sensory representation of the small-diameter afferent activity that relates to the physiological condition of the entire body. This cortical region seems to constitute a primary interoceptive image of homeostatic afferents. Embedded in the interoceptive cortex are the cortical representations of several highly resolved, distinct sensations, including temperature, pain, itch, muscular and visceral sensations, sensual touch and other feelings from the body. The importance of the interoceptive cortex for physical well-being is underscored by its clear delimitation in the monkey by *in situ* hybridization labelling for the mRNA of receptors for

corticotropin-releasing factor, which is thought by many to be a definitive indicator of an association with homeostatic stress[103].

Notably, the absence of this direct interoceptive representation in sub-primates implies that they cannot experience feelings from the body in the same way that humans do. In humans, lesions of the dorsal insula interrupt these feelings[83,84], disrupt homeostatic processing[104] and cause permanent loss of discriminative thermal sensation. By contrast, in cats that have been trained on a high-resolution thermosensory discrimination task, lesions of the rudimentary thalamocortical lamina I relay cause only a weak, transient behavioural deficit, whereas a spinal lesion of the ascending lamina I axons causes permanent disruption[105]. These findings indicate that behaviour in sub-primates reflects motivational signals from homeostatic integration centres in the brainstem and hypothalamus, and they reveal that homeostatic integration in the brainstem parabrachial nucleus is sufficient to motivate thermoregulatory behaviour. Indeed, in humans, a lesion of the lamina I spinothalamocortical pathway that eliminates thermal (and evoked pain) sensation can result in the central pain syndrome (BOX 2), which probably reflects a similar motivational signal to forebrain behavioural mechanisms by brainstem homeostatic drives that are released from descending insular cortical modulation[5,6,106]. The occurrence of central pain after lesions that disrupt evoked pain sensibility was a key argument made against the existence of a specific neural representation of pain[13]; however, the available evidence indicates that central pain can be regarded as thermoregulatory distress, consistent with the recognition that pain is both an aspect of interoception and a behavioural drive caused by a physiological imbalance that homeostatic systems alone cannot rectify.

So, like other feelings from the body, pain normally consists of both a sensation and a motivation. The cortical region associated with such motivation seems to be the anterior cingulate cortex (ACC). The insula has long been regarded as limbic sensory cortex, because of its association with visceral sensation by Penfield's stimulation studies in humans, whereas the ACC can be regarded as limbic motor cortex, because of its association with autonomic and emotional control[107,108]. Both are strongly interconnected with the amygdala, hypothalamus, orbitofrontal cortex and brainstem homeostatic regions[109,110]. Many recent functional imaging studies have documented the role of the ACC in behavioural drive and volition[111–113]. A particular portion of the ACC is activated in virtually all studies of pain[89,90,114]. The ACC is activated selectively during the thermal-grill illusion of pain, and therefore signifies the urgency of thermal distress[63]; similarly, the unpleasantness of thermal pain has been directly correlated with ACC activation using hypnotic manipulation[115]. In primates, the underlying pathway seems to be an ancillary lamina I spinothalamocortical route through the ventral caudal portion of the medial dorsal nucleus[6], where convergence with input from the parabrachial nucleus and other brainstem homeostatic sites seems likely[116]. Like the lamina I pathway to VMpo, this direct medial pathway to the ACC does not exist in sub-primates, in which a phylogenetically earlier lamina I projection is relayed by the thalamic submedial nucleus to the orbitofrontal cortex[6]. Although the underlying anatomy differs, data from studies in rats support a primordial role of the ACC in behavioural motivation by homeostatic distress, probably due to

Box 2 | **Central pain syndrome**



Damage to the brain can cause the central pain syndrome, in which ongoing, intractable pain is referred to contralateral deep and cutaneous tissues, where there is always a loss of thermal (cool and warm) sensation and often a paradoxical loss of acute pain (pinprick and heat) sensation[6,158]. Central pain is characteristically described as burning and hyperpathic (augmenting), and is often accompanied by mechanical or thermal (cold) allodynia — that is, pain is evoked by normally innocuous stimuli. It apparently results from damage to the lamina I spinothalamocortical pathway at any level, including interoceptive cortex, but it is not produced by lesions of the exteroceptive lemniscal pathways, the parietal somatosensory cortices or the medial thalamus. It occurs in ~5% of stroke patients and 25–40% of patients with multiple sclerosis or spinal cord injury. Tricyclic antidepressants are efficacious for about half of patients with central pain, but opiates are usually ineffective. Head and Holmes[12] first postulated that this is a release phenomenon that results from loss of an inhibitory effect of discriminative pain processing on the emotional aspect of pain, and others suggested release of phylogenetically old brainstem inputs or hyperactive bursting in somatosensory pathways. A recent proposal, the thermosensory-inhibition hypothesis, is based on the anatomy of the lamina I projection system. This hypothesis posits that central pain results from the loss of descending controls from interoceptive cortex on brainstem homeostatic sites that drive thermoregulatory behaviour by way of the medial thalamus and the anterior cingulate cortex (see figure; minus symbols denote inhibition). The disinhibition proposed by this hypothesis is conceptually similar to the unmasking shown by the thermal-grill illusion (BOX 1). This proposal views central pain as a thermoregulatory dysfunction, and it emphasizes the concept that pain is not only a feeling, but also a behavioural drive that signals a homeostatic imbalance.

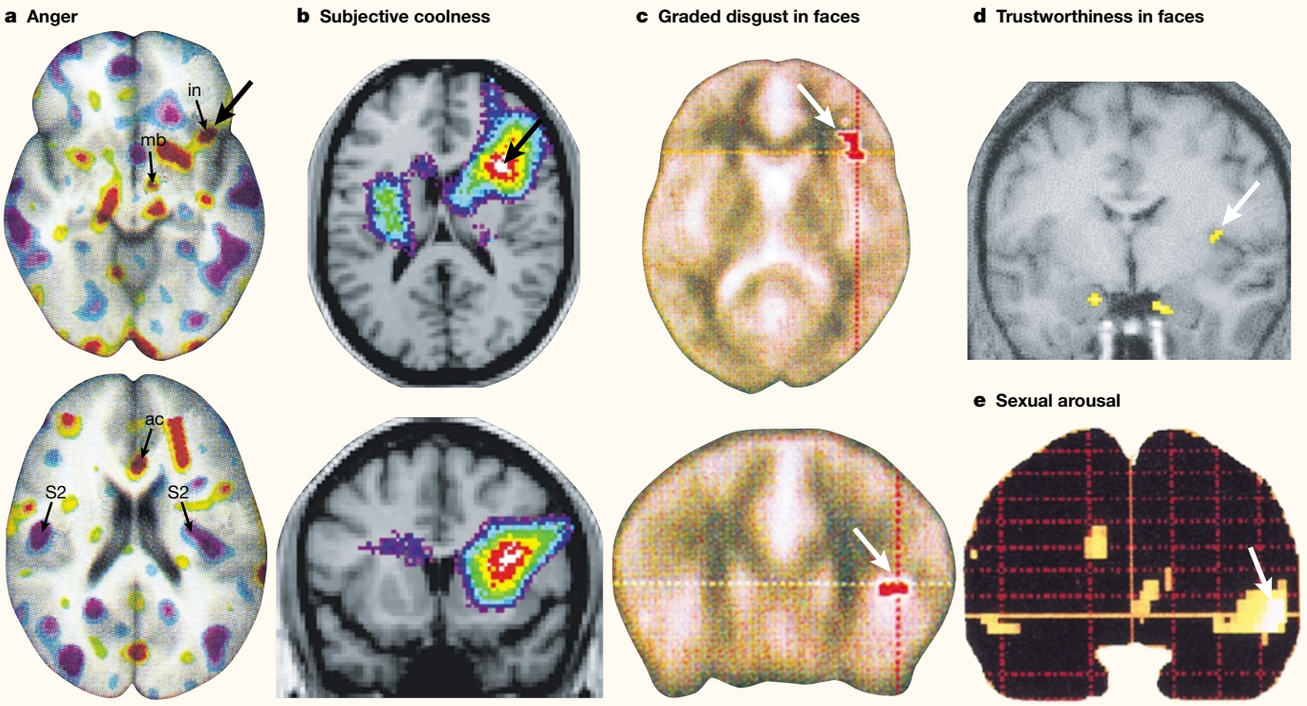


Figure 5 | **Activation of the right (non-dominant) anterior insular cortex associated with different subjective feelings. a** | Recall-induced anger, in which activation is also visible in the right orbitofrontal, anterior cingulate (ac) and interoceptive (S2) cortices (reproduced from REF. 123 © 2000 Macmillan Magazines Ltd). in, insular cortex; mb, mammillary bodies. **b** | Regression analysis of subjective ratings of the intensity of cooling the hand (reproduced from REF. 5 © 2000 Macmillan Magazines Ltd). **c** | Activation after exposure to graded disgust in computer-generated faces (reproduced from *Nature* (REF. 124) © 1997 Macmillan Magazines Ltd). **d** | Activation elicited by subjective ratings of trustworthiness in faces (reproduced from REF. 129 © 2002 Macmillan Magazines Ltd). **e** | Activation elicited by sexual arousal (reproduced, with permission, from REF. 128 © 1999 Kluwer Academic Publishers).

parabrachial and other brainstem inputs[117,118]. So, activation of the ACC is associated with motivation, and activation of the insula is associated with feeling, which together form an emotion.

Subjective awareness of feelings

How do we perceive the feelings from our bodies? We examined this question in our PET study of innocuous thermal sensibility[5], in which human volunteers provided a subjective magnitude rating of the perceived intensity of each stimulus (irrespective of emotional valence). Their ratings were not perfectly correlated with stimulus temperature, and regression analysis of these percepts showed strongly correlated activity in the right (ipsilateral, non-dominant) anterior insula (FIG. 5) and the orbitofrontal cortex, which differed significantly from the linear representation of stimulus temperature in the interoceptive cortex. This revealed that subjective evaluation of the thermal stimuli — the feeling elicited in each person by the graded coolness — depended on post-processing in those cortical regions. Close inspection of the correlation maps (see figure 2 in REF. 5, levels 20–24 mm) provided direct evidence that the underlying anatomical pathway involves first the contralateral anterior insula, which must contain an initial re-representation of interoceptive cortex on the same side, and then, by way of a callosal pathway, a lateralized, second-order re-representation on the right side that is subsequently forwarded to orbitofrontal cortex. Recent fMRI data indicate precisely the same progression of insular activity for the subjective appreciation of pain[91]. Sequential cortical processing occurs in all sensory systems, and it seems reasonable to conclude that evolutionary development of such a progression for interoception would be advantageous for survival by differentiating and refining the representation of internal feelings. Analogous re-representation and lateralization of gustatory processing in the left anterior insular and orbitofrontal cortices in humans has been proposed on the basis of clinical findings[119], and corroborated by functional imaging[120].

These observations match a wide variety of functional imaging studies that have associated activation of right anterior insular and orbitofrontal cortices with subjective emotion, such as recall-generated sadness or anger, anticipatory anxiety and pain, panic, disgust, sexual arousal, trustworthiness and even subjective responses (positive or negative) to music[121–127] (FIG. 5). For example, anger was associated with activation in the right anterior insula and the orbitofrontal cortex, as well as in the interoceptive dorsal posterior insular region[123] (albeit labelled 'S2'). Activation correlated with the implicit level of disgust elicited by computer-generated facial expressions was shown in the anterior insular and orbitofrontal cortices on the right side[124], even though this emotion is usually regarded as a derivative of gustation. Sexual arousal elicited by erotic films (measured by testosterone release and intumescence) was strongly correlated with right anterior insular activation[128]. Subjective assessment of the trustworthiness of faces also activated right anterior insula[129], and such activation has been explicitly interpreted as representing the subjective feeling (or 'gut reaction') elicited by each face[130].

These convergent findings are consistent with the concept that the re-representation of the cortical image of the interoceptive condition of the body serves as a limbic sensory substrate for subjective feelings and emotions.

This fits the idea that the evaluation of the state of the body in response to a pertinent stimulus serves as the basis for emotional feelings — the James–Lange theory of emotion[3]. In particular, these data are consistent with the neurological hypothesis, based on analyses of clinical cases and imaging data, that the right (non-dominant) anterior insula is integral for the generation of the mental image of one's physical state, which underlies basic emotional states and is required for the motivation to make rational decisions that affect survival and quality of life — the essence of the 'somatic marker' hypothesis of consciousness[131] (see also REFS 99,132) (BOX 3). Indeed, Damasio explicitly suggested that a re-mapping of the representation of the state of the body (interoceptive sensation) could provide an 'as if' circuit that would allow the brain to judge and predict the effects of emotionally relevant stimuli on the body, which is what these functional anatomical data seem to indicate. So, a refined image of the state of the body seems to provide the basis for awareness of the physical self across time.

Nonetheless, it is equally important to recognize that the ACC (as well as subcortical structures, such as the amygdala and ventral striatum[133–136]) is co-activated with the anterior insula in virtually all imaging studies of emotion[111,112,121,123,127,137], consistent with the view that an emotion is both a feeling and a motivation. Notably, this provides the active agent that is missing from the somatic-marker hypothesis, in which Damasio conjectured that the subjective 'I' is generated only as an illusory by-product of the re-mapping. For example, a recent imaging study of placebo analgesia revealed concomitant activation of both the ACC and the right anterior insula[138]; according to the present interpretation, this reflects the active modulation by the behaviourally motivating agent (limbic motor cortex, the ACC) of the feeling represented by the image of the expected state of the body (in the right anterior insula). This interpretation is consistent both with the interoceptive lamina I spinothalamocortical projections and with the overall anatomical organization of primate frontal cortex into medial (motor) and orbital (sensory) networks[139,140].

The orbitofrontal cortex, which correlated most strongly with subjective thermal perception[5], is associated with the discrimination of positive and negative rewards (pleasantness/unpleasantness, or hedonic valence, corresponding to approach/avoidance encoding) in relation to the body's needs[136,141,142]. For example, this region engenders stimulus-specific satiety to food[143], so it would probably also differentiate the affect associated with a thermal stimulus, or any other bodily feeling, according to the body's homeostatic needs. In fact, the orbitofrontal cortex guides feeding behaviour and behavioural valence in the rat as well; it is not a phylogenetically recent development. Anatomical data in the macaque monkey indicate that this region receives convergent input from several sensory systems, and it seems to receive a direct projection from gustatory and interoceptive insular cortex[133]. In other words, whereas the macaque monkey has an anatomically visible interoceptive thalamocortical pathway, it has direct interoceptive cortical projections to orbitofrontal cortex, and therefore might not have the intervening re-representations of the subjective state of the body in the right anterior insular cortex that are clearly present in humans.

These functional anatomical considerations indicate clearly that primates differ from sub-primates in the encephalization of a direct cortical image of the physiological condition of the body. Furthermore, they strongly suggest that humans differ from monkeys not only in the relative size of the interoceptive thalamocortical pathway, but also in the development of sequential re-representations of the physiological state of the body in the right anterior insula. The interoceptive re-representation that is lateralized in the right anterior insula of humans corresponds with the ability to perceive the self as a physical and separate entity — that is, self-awareness. The functional imaging data strongly support the integral role of the right anterior insula in the feelings we perceive that are the basis of our perceptions of our selves, and therefore of consciousness. As Damasio[131] has elegantly described, this level of consciousness is more than a basic sensory awareness of the environment. It is required for extended autobiographical and cognitive continuity, because it engenders the fundamental image of the physical self as a feeling (sentient) entity.

Conclusions and future directions

The identification of an entire neural system that can be cogently conceptualized as a representation of the physiological condition of the material body has several fundamental implications. It provides a rational explanation for the long-recognized association of pain, temperature, itch and other feelings from the body, separate from the lemniscal system that represents exteroceptive touch and proprioception. It incorporates specific labelled lines for several physical conditions that generate distinct feelings, and it substantiates their common integration in the hierarchical homeostatic network. It provides the long-missing peripheral and central afferent complement to the efferent autonomic nervous system. These findings reveal a direct cortical image of the state of the body that differentiates primates from sub-primates neuroanatomically. The size and multiple re-representations of this interoceptive image seem to differentiate humans from sub-human primates. Finally, these findings signify the cortical representation of feelings from the body as the likely basis for human awareness of the physical self as a feeling entity. This association provides a fundamental framework for the involvement of these feelings with emotion, mood, motivation and consciousness. These concepts emerge directly from the functional anatomy of the lamina I spinothalamocortical system, rather than from preconceived ideas.

Box 3 | The 'somatic marker' hypothesis of consciousness

On the basis of neurological analyses of patients with forebrain lesions, Antonio Damasio[123,131] has advanced the 'somatic marker' hypothesis of consciousness. He proposes that the subjective process of feeling emotions requires the participation of brain regions that are involved in the mapping and/or regulation of our continuously changing internal states — that is, in homeostasis. These feelings help to guide behavioural decisions that affect survival and quality of life by producing a 'perceptual landscape' that represents the emotional significance of a particular stimulus that is being experienced, or of a projected future action by means of a further 'as-if-body loop' mechanism. The feelings are grounded in the body itself, based on multi-tiered and evolutionarily developed neural mechanisms that control the body's state. These feelings distinguish between inner-world representations and outer-world representations, and allow the brain to build a meta-representational model of the relationship between outer and inner entities[159]. So, the representational image of the body's state provides a neural basis for distinguishing self from non-self, and re-representations of this image enable the behavioural neural agent to project the effects of possible actions onto the state of the body, as well as the resultant changes in such feeling states due to interactions with other (external) agents. This hypothesis posits that degrees of conscious awareness are related to successive upgrades in the self-representational maps[159]. The anatomical features of Damasio's hypothesis include a central role for the anterior insular cortex in the representation of such feeling states.

Glossary

AIR HUNGER
Hypercapnia with mechanically restricted ventilation.

ERGORECEPTION
Afferent activity relating tissue energy and metabolic needs.

EXERCISE PRESSOR REFLEX
Increased blood pressure and heart rate caused by activity in small-diameter afferents from muscle.

FIRST PAIN
Sharp, pricking pain associated with rapidly conducting Aδ-fibres.

LABELLED LINES
Anatomically and physiologically distinct neurons that are specifically associated with particular sensations.

NEUROPATHIC PAIN
Intractable pain associated with damage to the peripheral or central nervous system.

SECOND PAIN
Dull, burning pain associated with slowly conducting C-fibres.

TRIADIC ARRANGEMENT
Ultrastructural contacts between an afferent terminal, a relay cell dendrite and a GABA-containing presynaptic dendrite that is characteristic of high-fidelity transmission in sensory relay nuclei.

It is important to recognize that this neural sensory system is part of an entire network involved in homeostasis; that is, in the autonomic, hormonal and behavioural neural mechanisms that maintain optimal physiological conditions in the body and that respond in an integrated and ongoing fashion to all interior and exterior environmental challenges, ranging from exercise, dehydration or altitude to injury, sepsis or social interactions. The organization of this network is focused at the spinal level on cardiovascular and direct end-organ control[11,144], at the brainstem level on integrated control of fluid, electrolyte, energy, immune and cardiorespiratory balances[44,145], at the forebrain level in sub-primates on neuroendocrine and behavioural control[146,147], and in primates in a high-resolution encephalized representation of all aspects of the condition of the tissues. Nevertheless, it is a vertically integrated system, and it is important to recognize that the basis for feelings from the body in humans is this hierarchical association with homeostatic mechanisms[131,148]. This hypothesis is supported by the close correlation of brainstem activity with these subjective feelings in human imaging studies[5,123,148]. This recognition recommends analysis of the interactions of feelings and emotion with many aspects of subconscious homeostasis; for example, in stress or pain or cognitive behavioural research.

In contrast to the many discriminable sensations from the body, the subjective appreciation of visceral sensation is more diffuse, less well localized, and usually below perceptive thresholds. This was one of the main reasons for the long-standing mis-categorization of pain and temperature as exteroceptive rather than interoceptive. Although it would be highly inefficient for gastrointestinal processing to require constant behavioural supervision, this perceptual difference remains to be explained adequately[11]. Notably, many observations indicate that there is opponent processing between parasympathetic and sympathetic afferents that parallels their efferent opponency. For example, there are obligatory mutual inhibitory interactions between spinal and vagal small-diameter afferent activities in the medulla that are essential for cardiorespiratory control[149,150]. Similarly, vagal afferent activation inhibits both pain sensation[151] and spinal viscerceptive processing[152]. Vagal stimulation can reportedly reduce stress and depression clinically. Similarly, opposing effects on autonomic function have been elicited by stimulation of human insular cortex on both sides[153], and corresponding cortical lateralization has been observed with micturition[154] and gustation[120]. Such a basic organization would be parsimonious with many considerations and could explain the perceptual differences, but this certainly needs further study, particularly because of the potential clinical significance[155].

The association of the re-representation of the interoceptive pathway with self-awareness implies the existence of neuroanatomically verifiable correlates of conscious behaviour. To this end, we are now comparing the size and cytoarchitectonic differentiation of the thalamic relay VMpo in different primate species. Preliminary observations are supportive; VMpo in the pygmy chimpanzee, which can recognize itself in a mirror[156], is clearly similar to that in the human, albeit considerably smaller. By contrast, VMpo in the gibbon, which cannot recognize itself, is barely recognizable, like that in the macaque. Similarly, a unique cytological feature has been described in the ACC and the anterior insula of human and higher sub-human primates that is not present in lower animals[157]. Further anatomical analyses of the interoceptive cortex in sub-human primates and of the anterior insula in humans are certainly needed, and correlative imaging and clinical approaches would be most useful.

Finally, this conceptual framework has strong implications for medicine. The integrated neural representation of all aspects of the condition of the body in a system responsible for homeostasis and associated with stress — including a direct cortical image of physical well-being — provides a sound epistemological foundation for integrated approaches to the treatment of pain, metabolic, eating and psychosomatic disorders. For example, this provides an easy formulation for somatization under emotional stress. Similarly, these considerations imply that mysterious pain syndromes, such as fibromyalgia (deep aches and pains), could be related to homeostatic dysfunction (for example, salt or water balance or cardiovascular function), rather than to tissue damage, and this possibility deserves vigorous study. Consideration of these findings led directly to the recent proposal that the central pain syndrome is a thermoregulatory disorder[5,106]. The recognition that sensual touch is incorporated into the interoceptive system has strong implications for the neurobiological and health effects of conspecific contact — visitors to zoos will remember that monkeys, chimpanzees and bonobos normally spend an enormous amount of time grooming and cuddling each other, and readers will remember the classic studies by H. Harlow showing the importance of conspecific contact for emotional development. Last, the observation that the neuroanatomical substrate for subjective emotion in humans is based on an abstracted meta-representation of the physiological state of the body, consistent with the conjectures of James[3] and Damasio[131], provides a basis for the volitional modulation of feelings, emotion and efferent activity affecting the state of the body that is unique to humans[138], and clearly emphasizes the role of the body's health in human consciousness and interaction.

A. D. (Bud) Craig is at the Atkinson Pain Research Laboratory, Division of Neurosurgery, Barrow Neurological Institute, Phoenix, Arizona 85013, USA.
e-mail: bcraig@chw.edu

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1. Weber, E. H. *Handwörterbuch des Physiologie mit Rücksicht auf physiologische Pathologie* Bd 3, Abt 2 (ed. Wagner, R.) 481–588 (Biewig und Sohn, Braunschweig, Germany, 1846).
2. Sherrington, C. S. *Text-book of Physiology* (ed. Schäfer, E. A.) 920–1001 (Pentland, Edinburgh, UK, 1900).
3. James, W. *The Principles of Psychology* [online] <http://psychclassics.yorku.ca/James/Principles/index.htm> (1890).
4. Sherrington, C. S. *The Integrative Action of the Nervous System* (Cambridge Univ. Press, Cambridge, UK, 1948).
5. Craig, A. D., Chen, K., Bandy, D. & Reiman, E. M. Thermosensory activation of insular cortex. *Nature Neurosci.* **3**, 184–190 (2000).
6. Craig, A. D. *Nervous System Plasticity and Chronic Pain* (eds Sandkühler, J., Bromm, B. & Gebhart, G. F.) 137–151 (Elsevier, Amsterdam, 2000).
7. Craig, A. D. *The Emotional Motor System* (eds Holstege, G., Bandler, R. & Saper, C. B.) 225–242 (Elsevier, Amsterdam, 1996).
8. Bonica, J. J. *The Management of Pain* (ed. Bonica, J. J.) 28–95 (Lea & Fibiger, Philadelphia, Pennsylvania, 1990).
9. Willis, W. D. & Westlund, K. N. Neuroanatomy of the pain system and of the pathways that modulate pain. *J. Clin. Neurophysiol.* **14**, 2–31 (1997).

10. Cechetto, D. F. & Saper, C. B. *Central Regulation of Autonomic Function* (eds Loewy, A. D. & Spyer, K. M.) 208–223 (Oxford Univ. Press, New York, 1990).
11. Cameron, O. G. *Visceral Sensory Neuroscience* (Oxford Univ. Press, Oxford, UK, 2002).
12. Head, H. & Holmes, G. Sensory disturbances from cerebral lesions. *Brain* **34**, 102–254 (1911).
13. Melzack, R. & Wall, P. D. Pain mechanisms: a new theory. *Science* **150**, 971–979 (1965).
14. Price, D. D. & Dubner, R. Neurons that subserve the sensory-discriminative aspects of pain. *Pain* **3**, 307–338 (1977).
15. Cannon, W. B. *The Wisdom of the Body* (Norton & Co., New York, 1939).
16. May, W. P. The afferent path. *Brain* **29**, 742–803 (1906).
17. Bishop, G. H. The relation between nerve fiber size and sensory modality: phylogenetic implications of the afferent innervation of cortex. *J. Nerv. Ment. Dis.* **128**, 89–114 (1959).
18. Melzack, R. & Casey, K. L. *The Skin Senses* (ed. Kenshalo, D. R.) 423–443 (Thomas, Springfield, Illinois, 1968).
19. Cabanac, M. Preferred skin temperature as a function of internal and mean skin temperature. *J. Appl. Physiol.* **33**, 699–703 (1972).
20. Mower, G. Perceived intensity of peripheral thermal stimuli is independent of internal body temperature. *J. Comp. Physiol. Psychol.* **90**, 1152–1155 (1976).
21. Blatteis, C. M. (ed.) *Physiology and Pathophysiology of Temperature Regulation* (World Scientific, Singapore, 1998).
22. Satinoff, E. Neural organization and evolution of thermal regulation in mammals. *Science* **201**, 16–22 (1978).
23. Altman, J. & Bayer, S. A. The development of the rat spinal cord. *Adv. Anat. Embryol. Cell Biol.* **85**, 1–164 (1984).
24. Chen, Z. F. *et al.* The paired homeodomain protein DRG11 is required for the projection of cutaneous sensory afferent fibers to the dorsal spinal cord. *Neuron* **31**, 59–73 (2001).
25. Woodbury, C. J., Ritter, A. M. & Koerber, H. R. Central anatomy of individual rapidly adapting low-threshold mechanoreceptors innervating the 'hairy' skin of newborn mice: early maturation of hair follicle afferents. *J. Comp. Neurol.* **436**, 304–323 (2001).
26. MacIver, M. B. & Tanelian, D. L. Activation of C fibers by metabolic perturbations associated with tourniquet ischemia. *Anesthesiology* **76**, 617–623 (1992).
27. Hill, J. M., Pickar, J. G., Parrish, M. D. & Kaufman, M. P. Effects of hypoxia on the discharge of group III and IV muscle afferents in cats. *J. Appl. Physiol.* **73**, 2524–2529 (1992).
28. Petho, G., Porszasz, R., Peitl, B. & Szolcsanyi, J. Spike generation from dorsal roots and cutaneous afferents by hypoxia or hypercapnia in the rat *in vivo*. *Exp. Physiol.* **84**, 1–15 (1999).
29. Cook, S. P. & McCleskey, E. W. Cell damage excites nociceptors through release of cytosolic ATP. *Pain* **95**, 41–47 (2002).
30. Carlton, S. M., Du, J., Zhou, S. & Coggeshall, R. E. Tonic control of peripheral cutaneous nociceptors by somatostatin receptors. *J. Neurosci.* **21**, 4042–4049 (2001).
31. Cervero, F. & Janig, W. Visceral nociceptors: a new world order? *Trends Neurosci.* **15**, 374–378 (1992).
32. Perl, E. R. *Neurobiology of Nociceptors* (eds Belmonte, C. & Cervero, F.) 5–36 (Oxford Univ. Press, Oxford, UK, 1996).
33. Iggo, A. Cutaneous mechanoreceptors with afferent C fibres. *J. Physiol. (Lond.)* **152**, 337–353 (1960).
34. Mense, S. & Meyer, H. Different types of slowly conducting afferent units in cat skeletal muscle and tendon. *J. Physiol. (Lond.)* **363**, 403–417 (1985).
35. Gybels, J., Handwerker, H. O. & VanHees, J. A comparison between the discharges of human nociceptive nerve fibres and the subject's ratings of his sensations. *J. Physiol. (Lond.)* **292**, 193–206 (1979).
36. Adreani, C. M. & Kaufman, M. P. Effect of arterial occlusion on responses of group III and IV afferents to dynamic exercise. *J. Appl. Physiol.* **84**, 1827–1833 (1998).
37. Schaible, H. G. & Schmidt, R. F. Activation of groups III and IV sensory units in medial articular nerve by local mechanical stimulation of knee joint. *J. Neurophysiol.* **49**, 35–44 (1983).
38. Vallbo, A. B., Olausson, H. & Wessberg, J. Unmyelinated afferents constitute a second system coding tactile stimuli of the human hairy skin. *J. Neurophysiol.* **81**, 2753–2763 (1999).
39. Light, A. R. & Willcockson, H. H. Spinal laminae I–II neurons in rat recorded *in vivo* in whole cell, tight seal configuration: properties and opioid responses. *J. Neurophysiol.* **82**, 3316–3326 (1999).
40. Craig, A. D. Propriospinal input to thoracolumbar sympathetic nuclei from cervical and lumbar lamina I neurons in the cat and the monkey. *J. Comp. Neurol.* **331**, 517–530 (1993).
41. Craig, A. D. Distribution of brainstem projections from spinal lamina I neurons in the cat and the monkey. *J. Comp. Neurol.* **361**, 225–248 (1995).
42. Miller, A. D. & Ruggiero, D. A. Emetic reflex arc revealed by expression of the immediate-early gene c-*fos* in the cat. *J. Neurosci.* **14**, 871–888 (1994).
43. Sato, A. & Schmidt, R. F. Somatosympathetic reflexes: afferent fibers, central pathways, discharge characteristics. *Physiol. Rev.* **53**, 916–947 (1973).
44. Buijs, R. M., Chun, S. J., Niijima, A., Romijn, H. J. & Nagai, K. Parasympathetic and sympathetic control of the pancreas: a role for the suprachiasmatic nucleus and other hypothalamic centers that are involved in the regulation of food intake. *J. Comp. Neurol.* **431**, 405–423 (2001).
45. Diesel, D. A., Tucker, A. & Robertshaw, D. Cold-induced changes in breathing pattern as a strategy to reduce respiratory heat loss. *J. Appl. Physiol.* **69**, 1946–1952 (1990).
46. Holstege, G. Direct and indirect pathways to lamina I in the medulla oblongata and spinal cord of the cat. *Prog. Brain Res.* **77**, 47–94 (1988).
47. Han, Z.-S., Zhang, E.-T. & Craig, A. D. Nociceptive and thermoreceptive lamina I neurons are anatomically distinct. *Nature Neurosci.* **1**, 218–225 (1998).
48. Craig, A. D., Krout, K. & Andrew, D. Quantitative response characteristics of thermoreceptive and nociceptive lamina I spinothalamic neurons in the cat. *J. Neurophysiol.* **86**, 1459–1480 (2001).
49. Craig, A. D. & Andrew, D. Responses of spinothalamic lamina I neurons to repeated brief contact heat stimulation in the cat. *J. Neurophysiol.* **87**, 1902–1914 (2002).
50. Andrew, D. & Craig, A. D. Responses of spinothalamic lamina I neurons to maintained noxious mechanical stimulation in the cat. *J. Neurophysiol.* **87**, 1889–1901 (2002).
51. Andrew, D. & Craig, A. D. Spinothalamic lamina I neurones selectively responsive to cutaneous warming in cats. *J. Physiol. (Lond.)* **537**, 489–495 (2001).
52. Craig, A. D. & Kniffki, K.-D. Spinothalamic lumbosacral lamina I cells responsive to skin and muscle stimulation in the cat. *J. Physiol. (Lond.)* **365**, 197–221 (1985).
53. Light, A. R. *The Initial Processing of Pain and Its Descending Control: Spinal and Trigeminal Systems* (Karger, Basel, Switzerland, 1992).
54. Cervero, F. & Tattersall, J. E. H. Somatic and visceral inputs to the thoracic spinal cord of the cat: marginal zone (lamina I) of the dorsal horn. *J. Physiol. (Lond.)* **383**, 383–395 (1987).
55. Andrew, D. & Craig, A. D. Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. *Nature Neurosci.* **4**, 72–77 (2001).
56. Gebhart, G. F. & Ness, T. J. Central mechanisms of visceral pain. *Can. J. Physiol. Pharmacol.* **69**, 627–634 (1991).
57. Foreman, R. D. Mechanisms of cardiac pain. *Annu. Rev. Physiol.* **61**, 143–167 (1999).
58. Rosas-Arellano, M. P., Solano-Flores, L. P. & Ciriello, J. c-Fos induction in spinal cord neurons after renal arterial or venous occlusion. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **276**, R120–R127 (1999).
59. Wilson, L. B., Andrew, D. & Craig, A. D. Activation of spinobulbar lamina I neurons by static muscle contraction. *J. Neurophysiol.* **87**, 1641–1645 (2002).
60. Milne, R. J., Foreman, R. D. & Willis, W. D. Responses of primate spinothalamic neurons located in the sacral intermediomedial gray (Stilling's nucleus) to proprioceptive input from the tail. *Brain Res.* **234**, 227–236 (1982).
61. Carstens, E. Responses of rat spinal dorsal horn neurons to intracutaneous microinjection of histamine, capsaicin, and other irritants. *J. Neurophysiol.* **77**, 2499–2514 (1997).
62. Craig, A. D. & Bushnell, M. C. The thermal grill illusion: unmasking the burn of cold pain. *Science* **265**, 252–255 (1994).
63. Craig, A. D., Reiman, E. M., Evans, A. & Bushnell, M. C. Functional imaging of an illusion of pain. *Nature* **384**, 258–260 (1996).
64. Yarnitsky, D. & Ochoa, J. L. Release of cold-induced burning pain by block of cold-specific afferent input. *Brain* **113**, 893–902 (1990).
65. Sinoway, L. I., Hill, J. M., Pickar, J. G. & Kaufman, M. P. Effects of contraction and lactic acid on the discharge of group III muscle afferents in cats. *J. Neurophysiol.* **69**, 1053–1059 (1993).
66. Pickar, J. G., Hill, J. M. & Kaufman, M. P. Dynamic exercise stimulates group III muscle afferents. *J. Neurophysiol.* **71**, 753–760 (1994).
67. LeDoux, J. F. & Wilson, L. B. Neuronal application of capsaicin modulates somatic pressor reflexes. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **281**, R868–R877 (2001).
68. Simone, D. A., Marchettini, P., Caputi, G. & Ochoa, J. L. Identification of muscle afferents subserving sensation of deep pain in humans. *J. Neurophysiol.* **72**, 883–889 (1994).
69. Villanueva, L. & Nathan, P. W. in *Proc. 9th World Congr. Pain* (eds Devor, M., Rowbotham, M. C. & Wiesenfeld-Hallin, Z.) 371–386 (IASP Press, Seattle, Washington, 2000).
70. Craig, A. D., Bushnell, M. C., Zhang, E.-T. & Blomqvist, A. A thalamic nucleus specific for pain and temperature sensation. *Nature* **372**, 770–773 (1994).
71. Blomqvist, A., Zhang, E. T. & Craig, A. D. Cytoarchitectonic and immunohistochemical characterization of a specific pain and temperature relay, the posterior portion of the ventral medial nucleus, in the human thalamus. *Brain* **123**, 601–619 (2000).
72. Blomqvist, A., Ericson, A. C., Craig, A. D. & Broman, J. Evidence for glutamate as a neurotransmitter in spinothalamic tract terminals in the posterior region of owl monkeys. *Exp. Brain Res.* **108**, 33–44 (1996).
73. Beckstead, R. M., Morse, J. R. & Norgren, R. The nucleus of the solitary tract in the monkey: projections to the thalamus and brain stem nuclei. *J. Comp. Neurol.* **190**, 259–282 (1980).
74. Burstein, R. Somatosensory and visceral input to the hypothalamus and limbic system. *Prog. Brain Res.* **107**, 257–267 (1996).
75. Craig, A. D., Zhang, E. T. & Blomqvist, A. A distinct thermoreceptive subregion of lamina I in nucleus caudalis of the owl monkey. *J. Comp. Neurol.* **404**, 221–234 (1999).
76. Lenz, F. A. *et al.* Neurons in the area of human thalamic nucleus ventralis caudalis respond to painful heat stimuli. *Brain Res.* **623**, 235–240 (1993).
77. Davis, K. D. *et al.* Thalamic relay site for cold perception in humans. *J. Neurophysiol.* **81**, 1970–1973 (1999).
78. Dostrovsky, J. O., Wells, F. E. B. & Tasker, R. R. in *Processing and Inhibition of Nociceptive Information, Int. Congr. Ser. 989* (eds Inoka, R., Shigenaga, Y. & Tohyama, M.) 115–120 (Excerpta Medica, Amsterdam, 1992).
79. Lenz, F. A. *et al.* The sensation of angina can be evoked by stimulation of the human thalamus. *Pain* **59**, 119–125 (1994).
80. Lenz, F. A. *et al.* Thermal and pain sensations evoked by microstimulation in the area of human ventrocaudal nucleus. *J. Neurophysiol.* **70**, 200–212 (1993).
81. Pritchard, T. C., Hamilton, R. B., Morse, J. R. & Norgren, R. Projections of thalamic gustatory and lingual areas in the monkey, *Macaca fascicularis*. *J. Comp. Neurol.* **244**, 213–228 (1986).
82. Yaxley, S., Rolls, E. T. & Sienkiewicz, Z. J. Gustatory responses of single neurons in the insula of the macaque monkey. *J. Neurophysiol.* **63**, 689–700 (1990).
83. Schmahmann, J. D. & Leifer, D. Parietal pseudothalamic pain syndrome: clinical features and anatomic correlates. *Arch. Neurol.* **49**, 1032–1037 (1992).
84. Greenspan, J. D. & Winfield, J. A. Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum. *Pain* **50**, 29–39 (1992).
85. Burton, H. & Jones, E. G. The posterior thalamic region and its cortical projection in new world and old world monkeys. *J. Comp. Neurol.* **168**, 249–302 (1976).
86. Disbrow, E., Roberts, T. & Krubitzer, L. Somatotopic organization of cortical fields in the lateral sulcus of *Homo sapiens*: evidence for SII and PV. *J. Comp. Neurol.* **418**, 1–21 (2000).
87. Hofbauer, R. K., Rainville, P., Duncan, G. H. & Bushnell, M. C. Cortical representation of the sensory dimension of pain. *J. Neurophysiol.* **86**, 402–411 (2001).
88. Coghill, R. C., Sang, C. N., Maisog, J. H. & Iadarola, M. J. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J. Neurophysiol.* **82**, 1934–1943 (1999).
89. Derbyshire, S. W. G. & Jones, A. K. P. Cerebral responses to a continual tonic pain stimulus measured using positron emission tomography. *Pain* **76**, 127–135 (1998).
90. Casey, K. L. Forebrain mechanisms of nociception and pain — analysis through imaging. *Proc. Natl Acad. Sci. USA* **96**, 7668–7674 (1999).
91. Brooks, J. C., Nurmikko, T. J., Bimson, W. E., Singh, K. D. & Roberts, N. fMRI of thermal pain: effects of stimulus laterality and attention. *Neuroimage* **15**, 293–301 (2002).
92. Kupers, R. C., Gybels, J. M. & Gjedde, A. Positron emission tomography study of a chronic pain patient

successfully treated with somatosensory thalamic stimulation. *Pain* **87**, 295–302 (2000).
93. Peyron, R. *et al.* Parietal and cingulate processes in central pain. A combined positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) study of an unusual case. *Pain* **84**, 77–87 (2000).
94. Drzezga, A. *et al.* Central activation by histamine-induced itch: analogies to pain processing: a correlational analysis of O-15 H_2O positron emission tomography studies. *Pain* **92**, 295–305 (2001).
95. King, A. B., Menon, R. S., Hachinski, V. & Cechetto, D. F. Human forebrain activation by visceral stimuli. *J. Comp. Neurol.* **413**, 572–582 (1999).
96. Williamson, J. W., McColl, R., Mathews, D., Ginsburg, M. & Mitchell, J. H. Activation of the insular cortex is affected by the intensity of exercise. *J. Appl. Physiol.* **87**, 1213–1219 (1999).
97. Banzett, R. B. *et al.* Breathlessness in humans activates insular cortex. *Neuroreport* **11**, 2117–2120 (2000).
98. Tataranni, P. A. *et al.* Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. *Proc. Natl Acad. Sci. USA* **96**, 4569–4574 (1999).
99. Denton, D. *et al.* Neuroimaging of genesis and satiation of thirst and an interoceptor-driven theory of origins of primary consciousness. *Proc. Natl Acad. Sci. USA* **96**, 5304–5309 (1999).
100. Kinomura, S. *et al.* Functional anatomy of taste perception in the human brain studied with positron emission tomography. *Brain Res.* **659**, 263–266 (1994).
101. Olausson, H. *et al.* Unmyelinated tactile afferents in humans: functional role and cortical projections. *Nature Neurosci.* (doi:10.1038/nn896).
102. White, J. C. & Sweet, W. H. *Pain and the Neurosurgeon: a Forty-Year Experience* (Thomas, Springfield, Illinois, 1969).
103. Sanchez, M. M., Young, L. J., Plotsky, P. M. & Insel, T. R. Autoradiographic and *in situ* hybridization localization of corticotropin-releasing factor 1 and 2 receptors in nonhuman primate brain. *J. Comp. Neurol.* **408**, 365–377 (1999).
104. Appenzeller, O. & Oribe, E. *The Autonomic Nervous System: an Introduction to Basic and Clinical Concepts* (Elsevier, Amsterdam, 1997).
105. Norrsell, U. & Craig, A. D. Behavioral thermosensitivity after lesions of thalamic target areas of a thermosensory spinothalamic pathway in the cat. *J. Neurophysiol.* **82**, 611–625 (1999).
106. Craig, A. D. A new version of the thalamic disinhibition hypothesis of central pain. *Pain Forum* **7**, 1–14 (1998).
107. Mesulam, M.-M. & Mufson, E. J. Insula of the old world monkey. III. Efferent cortical output and comments on function. *J. Comp. Neurol.* **212**, 38–52 (1982).
108. Devinsky, O., Morrell, M. J. & Vogt, B. A. Contributions of anterior cingulate cortex to behaviour. *Brain* **118**, 279–306 (1995).
109. Yasui, Y., Breder, C. D., Saper, C. B. & Cechetto, D. F. Autonomic responses and efferent pathways from the insular cortex in the rat. *J. Comp. Neurol.* **303**, 355–374 (1991).
110. Floyd, N. S., Price, J. L., Ferry, A. T., Keay, K. A. & Bandler, R. Orbitomedial prefrontal cortical projections to distinct longitudinal columns of the periaqueductal gray in the rat. *J. Comp. Neurol.* **422**, 556–578 (2000).
111. Frith, C. D. & Frith, U. Interacting minds — a biological basis. *Science* **286**, 1692–1695 (1999).
112. Paus, T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nature Rev. Neurosci.* **2**, 417–424 (2001).
113. Johnson, S. C. *et al.* Neural correlates of self-reflection. *Brain* (in the press).
114. Talbot, J. D. *et al.* Multiple representations of pain in human cerebral cortex. *Science* **251**, 1355–1358 (1991).
115. Rainville, P., Duncan, G. H., Price, D. D., Carrier, B. & Bushnell, M. C. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* **277**, 968–971 (1997).
116. Krout, K. E. & Loewy, A. D. Parabrachial nucleus projections to midline and intralaminar thalamic nuclei of the rat. *J. Comp. Neurol.* **428**, 475–494 (2000).
117. Johansen, J. P., Fields, H. L. & Manning, B. H. The affective component of pain in rodents: direct evidence for a contribution of the anterior cingulate cortex. *Proc. Natl Acad. Sci. USA* **98**, 8077–8082 (2001).
118. Gabriel, M., Kubota, Y., Sparenborg, S., Straube, K. & Vogt, B. A. Effects of cingulate cortical lesions on avoidance learning and training-induced unit activity in rabbits. *Exp. Brain Res.* **86**, 585–600 (1991).
119. Pritchard, T. C., Macaluso, D. A. & Eslinger, P. J. Taste perception in patients with insular cortex lesions. *Behav. Neurosci.* **113**, 663–671 (1999).
120. de Araujo, I. E. T., Kringelbach, M. L. & Rolls, E. T. Orbitofrontal cortex responses to the synergistic combination of umami stimuli. *Neuroimage* **13**, S967 (2002).
121. Reiman, E. M. The application of positron emission tomography to the study of normal and pathological emotions. *J. Clin. Psychiatry* **58**, 4–12 (1997).
122. Mayberg, H. S. *et al.* Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am. J. Psychiatry* **156**, 675–682 (1999).
123. Damasio, A. R. *et al.* Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neurosci.* **3**, 1049–1056 (2000).
124. Phillips, M. L. *et al.* A specific neural substrate for perceiving facial expressions of disgust. *Nature* **389**, 495–498 (1997).
125. Benkelfat, C. *et al.* Functional neuroanatomy of CCK4-induced anxiety in normal healthy volunteers. *Am. J. Psychiatry* **152**, 1180–1184 (1995).
126. Ploghaus, A. *et al.* Dissociating pain from its anticipation in the human brain. *Science* **284**, 1979–1981 (1999).
127. Blood, A. J. & Zatorre, R. J. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc. Natl Acad. Sci. USA* **98**, 11818–11823 (2001).
128. Stoleru, S. *et al.* Neuroanatomical correlates of visually evoked sexual arousal in human males. *Arch. Sex. Behav.* **28**, 1–21 (1999).
129. Winston, J. S., Strange, B. A., O'Doherty, J. & Dolan, R. J. Automatic and intentional brain responses during evaluation of trustworthiness of faces. *Nature Neurosci.* **5**, 277–283 (2002).
130. Adolphs, R. Trust in the brain. *Nature Neurosci.* **5**, 192–193 (2002).
131. Damasio, A. R. *Descartes' Error: Emotion, Reason, and the Human Brain* (Putnam, New York, 1993).
132. Farrer, C. & Frith, C. D. Experiencing oneself vs another person as being the cause of an action: the neural correlates of the experience of agency. *Neuroimage* **15**, 596–603 (2002).
133. Carmichael, S. T. & Price, J. L. Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. *J. Comp. Neurol.* **363**, 642–664 (1995).
134. Chikama, M., McFarland, N. R., Amaral, D. G. & Haber, S. N. Insular cortical projections to functional regions of the striatum correlate with cortical cytoarchitectonic organization in the primate. *J. Neurosci.* **17**, 9686–9705 (1997).
135. Becerra, L., Breiter, H. C., Wise, R., Gonzalez, R. G. & Borsook, D. Reward circuitry activation by noxious thermal stimuli. *Neuron* **32**, 927–946 (2001).
136. O'Doherty, J., Rolls, E. T., Francis, S., Bowtell, R. & McGlone, F. Representation of pleasant and aversive taste in the human brain. *J. Neurophysiol.* **85**, 1315–1321 (2001).
137. Bartels, A. & Zeki, S. The neural basis of romantic love. *Neuroreport* **11**, 3829–3834 (2000).
138. Petrovic, P., Kalso, E., Petersson, K. M. & Ingvar, M. Placebo and opioid analgesia — imaging a shared neuronal network. *Science* **295**, 1737–1740 (2002).
139. Carmichael, S. T. & Price, J. L. Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *J. Comp. Neurol.* **371**, 179–207 (1996).
140. Ongur, D. & Price, J. L. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb. Cortex* **10**, 206–219 (2000).
141. Francis, S. *et al.* The representation of pleasant touch in the brain and its relationship with taste and olfactory areas. *Neuroreport* **10**, 453–459 (1999).
142. Royet, J. P. *et al.* Emotional responses to pleasant and unpleasant olfactory, visual, and auditory stimuli: a positron emission tomography study. *J. Neurosci.* **20**, 7752–7759 (2000).
143. Rolls, E. T. *The Brain and Emotion* (Oxford Univ. Press, Oxford, UK, 1999).
144. Janig, W. Neurobiology of visceral afferent neurons: neuroanatomy, functions, organ regulations and sensations. *Biol. Psychol.* **42**, 29–51 (1996).
145. Loewy, A. D. & Spyer, K. M. *Central Regulation of Autonomic Functions* (Oxford, New York, 1990).
146. Sawchenko, P. E. *et al.* in *The Emotional Motor System* (eds Holstege, G., Bandler, R. & Saper, C. B.) 201–224 (Elsevier, Amsterdam, 1996).
147. Swanson, L. W. Cerebral hemisphere regulation of motivated behavior. *Brain Res.* **886**, 113–164 (2000).
148. Critchley, H. D., Mathias, C. J. & Dolan, R. J. Neuroanatomical basis for first- and second-order representations of bodily states. *Nature Neurosci.* **4**, 207–212 (2001).
149. Potts, J. T. Exercise and sensory integration. Role of the nucleus tractus solitarius. *Ann. NY Acad. Sci.* **940**, 221–236 (2001).
150. Zagon, A. Does the vagus nerve mediate the sixth sense? *Trends Neurosci.* **24**, 671–673 (2001).
151. Ness, T. J., Fillingim, R. B., Randich, A., Backensto, E. M. & Faught, E. Low intensity vagal nerve stimulation lowers human thermal pain thresholds. *Pain* **86**, 81–85 (2000).
152. Chandler, M. J., Zhang, J., Qin, C. & Foreman, R. D. Spinal inhibitory effects of cardiopulmonary afferent inputs in monkeys: neuronal processing in high cervical segments. *J. Neurophysiol.* **87**, 1290–1302 (2002).
153. Oppenheimer, S. The anatomy and physiology of cortical mechanisms of cardiac control. *Stroke* **24**, I3–I5 (1993).
154. Blok, B. F. M., Willemsen, A. T. M. & Holstege, G. A PET study on brain control of micturition in humans. *Brain* **120**, 111–121 (1997).
155. Saper, C. B. Pain as a visceral sensation. *Prog. Brain Res.* **122**, 237–243 (2000).
156. Macphail, E. M. *The Evolution of Consciousness* (Oxford Univ. Press, Oxford, UK, 1998).
157. Nimchinsky, E. A. *et al.* A neuronal morphologic type unique to humans and great apes. *Proc. Natl Acad. Sci. USA* **96**, 5268–5273 (1999).
158. Pagni, C. A. *Central Pain: a Neurosurgical Challenge* (Ediziona Minerva Medica S. P. A., Turin, 1998).
159. Churchland, P. S. Self-representation in nervous systems. *Science* **296**, 308–310 (2002).

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