ELSEVIER

Interoception: the sense of the physiological condition of the body
AD (Bud) Craig

Converging evidence indicates that primates have a distinct cortical image of homeostatic afferent activity that reflects all aspects of the physiological condition of all tissues of the body. This interoceptive system, associated with autonomic motor control, is distinct from the exteroceptive system (cutaneous mechanoreception and proprioception) that guides somatic motor activity. The primary interoceptive representation in the dorsal posterior insula engenders distinct highly resolved feelings from the body that include pain, temperature, itch, sensual touch, muscular and visceral sensations, vasomotor activity, hunger, thirst, and 'air hunger'. In humans, a meta-representation of the primary interoceptive activity is engendered in the right anterior insula, which seems to provide the basis for the subjective image of the material self as a feeling (sentient) entity, that is, emotional awareness.

Addresses
Atkinson Pain Research Laboratory, Division of Neurosurgery, Barrow Neurological Institute, Phoenix, AZ 85013, USA
e-mail: bcraig@chw.edu

Abbreviations
ACC anterior cingulate cortex
MDvc ventral caudal portion of the medial dorsal nucleus
NTS nucleus of the solitary tract
PB parabrachial nucleus
VMpo posterior ventral medial nucleus
VMb basal ventral medial nucleus

Introduction
Humans perceive 'feelings' from the body that provide a sense of their physical condition and underlie mood and emotional state. However, in the conventional view, the well-discriminated feelings of temperature, itch and pain are associated with an 'exteroceptive' somatosensory system, whereas the less distinct visceral feelings of vasomotor activity, hunger, thirst and internal sensations are associated with a separate 'interoceptive' system. That categorization obscures several fundamental discrepancies, such as the lack of effect of stimulation or lesions of somatosensory cortices on temperature or pain sensation, and the inherent emotional (affective/motivational) qualities and reflexive autonomic effects that all feelings from

the body share. Recent findings that compel a conceptual shift resolve these issues by showing that all feelings from the body are represented in a phylogenetically new system in primates. This system has evolved from the afferent limb of the evolutionarily ancient, hierarchical homeostatic system that maintains the integrity of the body. These feelings represent a sense of the physiological condition of the entire body, redefining the category 'interoception'. The present article summarizes this new view; more detailed reviews are available elsewhere [1••,2].
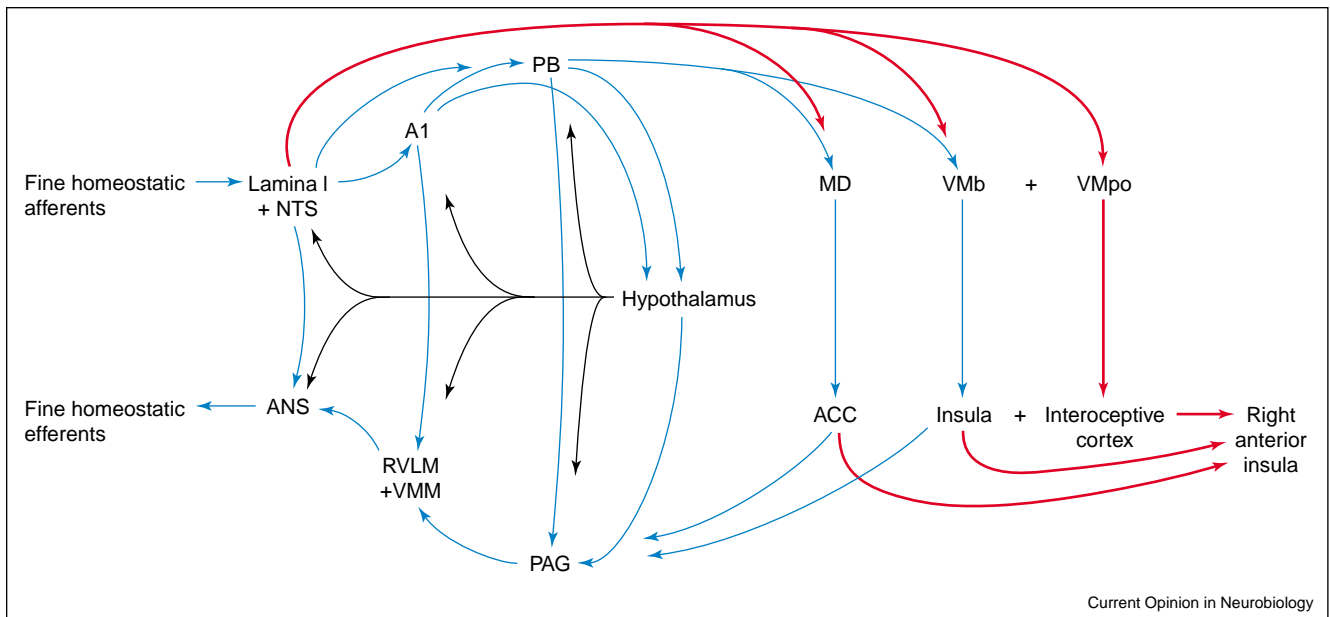
A homeostatic afferent pathway
Anatomical characteristics
Cannon [3] recognized that the neural processes (autonomic, neuroendocrine and behavioral) that maintain optimal physiological balance in the body, or homeostasis, must receive afferent inputs that report the condition of the tissues of the body. 'Parasympathetic' (vagal and glosso-pharyngeal) afferents to the nucleus of the solitary tract (NTS) have long been recognized, but an afferent pathway that parallels sympathetic efferents has only recently been identified. Small-diameter (Aδ and C) primary afferent fibers that innervate all tissues of the body terminate monosynaptically in lamina I of the spinal and trigeminal dorsal horns [1••,4]. Such fibers conduct information regarding all manner of physiological conditions, including the mechanical, thermal, chemical, metabolic and hormonal status of skin, muscle, joints, teeth and viscera. They are intimately linked developmentally with lamina I cells, which in contrast to the remainder of the dorsal horn arise from progenitors of autonomic interneurons, and together they form a cohesive afferent pathway [5]. Accordingly, the lamina I neurons in turn project densely to the autonomic cell columns, thus forming a spino-spinal loop for somato-autonomic reflexes [6]. Strikingly, lamina I and the autonomic cell columns are the only spinal targets of descending fibers from the hypothalamus [7].

Lamina I neurons also project densely and selectively to pre-autonomic sites in the brainstem, thus extending the afferent limb to the next rungs of the homeostatic hierarchy (Figure 1) and generating spino-bulbo-spinal loops for somato-autonomic reflexes [8,9]. These sites include the catecholamine cell groups; the strong input to the A1 group is particularly noteworthy, because its projections to the hypothalamus are crucial for neuroendocrine responses to changes in tissue conditions [1••,10]. The major target of lamina I and the NTS in the upper brainstem is the parabrachial nucleus (PB); the PB is the main integration site for all homeostatic afferent activity, and thus, it is essential for the maintenance of cardiovascular, respiratory, energy (feeding and glucose),

Figure 1

An organizational map of the homeostatic afferent system and its extension into the forebrain of primates. The afferent limb is shown in the top row and the efferent limb in the bottom row. The hierarchy consists of input-output loops at several levels, all of which are modulated by the hypothalamus (black lines) as well as the limbic sensory (insula) and limbic motor (cingulate) cortices (not shown). The red lines indicate the phylogenetically new pathways in primates that provide a direct thalamocortical input reflecting the physiological condition of the body. In humans, re-representations of the interoceptive cortex lead to a meta-representation of the state of the body in the right anterior insula that is associated with the subjective awareness of the 'feeling self'.

and fluid (electrolyte and water) balances [9,11]. The lamina I projections to the PB have been narrowly viewed by some as subserving nociception (sensory input caused by damaging stimuli). However, the integrative role of lamina I, NTS, and PB in the homeostatic afferent pathway is clearly consistent with the dense projections of PB to the periaqueductal gray (PAG; the mesencephalic homeostatic motor center) and to the hypothalamus (the diencephalic homeostatic motor center), which guide goal-directed autonomic, neuroendocrine and behavioral activity [11,12].

In all mammals, the integrated homeostatic afferent information from PB reaches the anterior cingulate (ACC) and insular cortices by way of the medial thalamic nuclei and the basal ventral medial nucleus (VMb) of the thalamus (also called the parvicellular ventroposteromedial nucleus), respectively [11,13]. Accordingly, multimodal context-dependent responses have been recorded in these regions in the rat [11,14]. The ACC (limbic motor cortex) and the insula (limbic sensory cortex) provide descending control of brainstem homeostatic integration sites, and lesions there disrupt homeostatic behavior [15,16•]. The emotional behavior of non-primate mammals suggests the anthropomorphic inference that they experience feelings from the body in the same way that humans do [17]. However, the neuroanatomical evidence indicates that

they cannot, because the phylogenetically new pathway that conveys primary homeostatic afferent activity directly to thalamocortical levels in primates (described below) is either rudimentary or absent in non-primates [1••].

Physiological characteristics
The Aδ and C primary afferent fibers respond to all manner of changes in the physiological condition of all tissues of the body (i.e. not just 'pain and temperature'); for example, C-fibers can respond to hypoxia, hypoglycemia, hypo-osmolarity, and the presence of muscle metabolic products [1••,18]. In addition, some C-fibers are exquisitely sensitive to light (sensual) touch [19]. Accordingly, lamina I neurons comprise several modality-selective, morphologically distinct classes that receive input from specific subsets of primary afferent fibers [2,20,21•,22•,23,24]. These classes can be differentiated on the basis of afferent responses, electrophysiological properties, axonal projections, descending modulation, and pharmacological properties, and they correspond psychophysically with distinct feelings from the body. They include cells selectively responsive to Aδ nociceptors (first, sharp pain), C-fiber nociceptors (second, burning pain), Aδ cooling-specific thermoreceptors (cool), C-fiber warming-specific receptors (warmth), ultra-slow histamine-selective C-fibers (itch), tactile C-fibers (sensual touch), and Aδ and C mechano- and metabo-receptors in muscles and

joints (muscle exercise, burn and cramp). Cells selectively responsive to subsets of visceral afferent fibers have not been well characterized for methodological reasons, but anatomical and psychophysical data also indicate that such specificity exists [2].

These distinct classes of neurons provide the substrate for the modality-selective somato-autonomic adjustments that are continually being made by homeostatic processes. For example, innocuous thermoreceptive (cool) activity linearly modulates respiratory parameters [25], consistent with the primordial role of thermoreception in homeostasis (i.e. thermoregulation). Similarly, muscle afferent activity modulates cardiovascular activity on an ongoing basis. The lamina I neurons that are directly related to human pain sensation are also essentially homeostatic in nature. In particular, the second (burning) pain sensation encoded by the C-fiber-selective poly-modal nociceptive lamina I cells is primarily a homeostatic afferent signal. Their ongoing activity is related to the strength of their C-fiber input [2], consistent with the hypothesis that such activity signals metabolic status on an ongoing basis. They are sensitive to noxious heat, pinch and noxious cold, but their static cold sensitivity begins at around 24°C (about 75°F), consistent with the increasing thermal discomfort that humans feel below that temperature. The burning pain generated by their activity depends on integration with the cooling-specific lamina I activity in the forebrain, as demonstrated by the thermal grill illusion (for an explanation of thermal grill illusion see Craig [1••]), and with core temperature [2], which directly implies that such thermal distress is a homeostatic behavioral motivation.

A distinct interoceptive pathway in primates
Input to VMpo
In primates, lamina I neurons project topographically to a relay nucleus in the posterolateral thalamus, the posterior ventral medial nucleus (VMpo) [1••,26]. Their axons ascend in the lateral spinothalamic tract, precisely where lesions selectively interrupt the feelings from the body [27]. The VMpo is organized antero-posteriorly, orthogonal to the medio-lateral topography of the somatosensory ventral posterior (VP) nuclei, which it is connected to at the point at which the mouth is represented. It adjoins anteriorly the basal ventral medial nucleus (VMb), which in primates receives direct input from NTS in addition to the integrated input it receives from PB in all mammals [28]. The VMpo is small in macaque monkeys, but in the human thalamus it is almost as large as the VP [29]. Calbindin-immunoreactivity makes the lamina I projection to VMpo discernible in both monkeys and humans (Figure 2).

The VMpo and VMb project topographically to interoceptive cortex in the dorsal margin of the insula (a cortical 'island' buried within the lateral sulcus that has intimate connections with the ACC, amygdala, hypothalamus, and

Figure 2
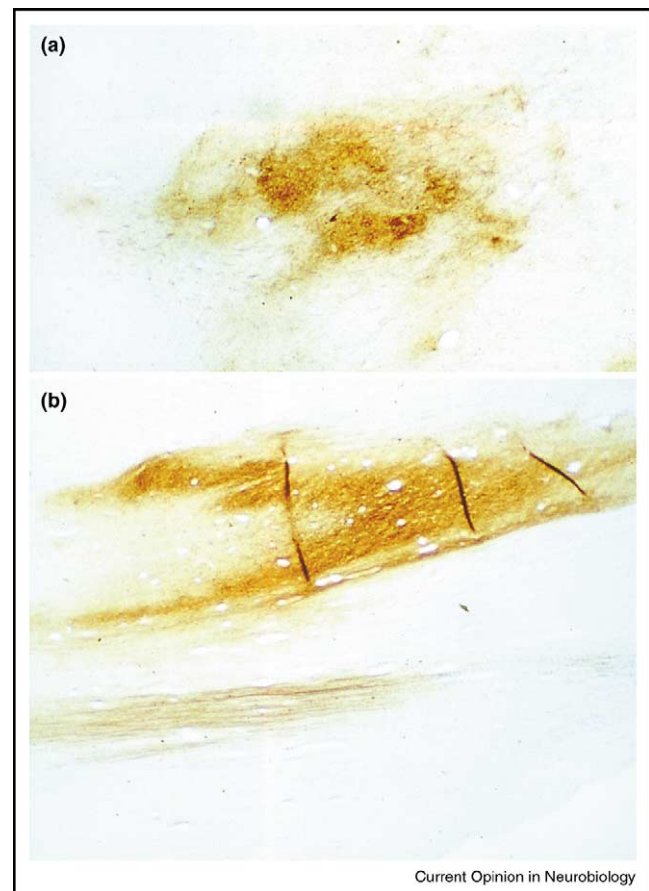
Immunohistochemical identification of the lamina I spinothalamic pathway in humans. Photomicrographs showing **(a)** calbindin-labeled lamina I terminations in the VMpo (coronal section) and **(b)** their ascending axons in the lateral spinothalamic tract (oblique transverse section) in humans. Note that the dense staining of the superficial dorsal horn, including lamina I neurons, in the upper half of (b).

orbitofrontal cortex) [30]. Converging functional imaging studies in monkeys and humans reveal that interoceptive cortex is activated in a graded manner by noxious stimuli (pain), temperature (Figure 3), itch, muscle exercise, cardiorespiratory activation, hunger, thirst, and sensual touch [1••,31,32•,33,34•]. This distinct cortical area is well-demarcated by *in situ* labeling for receptors of corticotropin releasing factor [35], consistent with a major role in homeostasis as limbic sensory cortex. Lesion, stimulation and evoked potential studies confirm the role of this primary cortical region in pain and temperature sensation and in autonomic function [2,36–38]. A corollary VMpo projection to area 3a in sensorimotor cortex may relate cutaneous pain to (exteroceptive) somatic motor activity [1••,2].

Input to MDvc
A direct lamina I pathway to the ACC is also present in primates by way of a topographic projection to the ventral caudal portion of the medial dorsal nucleus (MDvc)

Figure 3
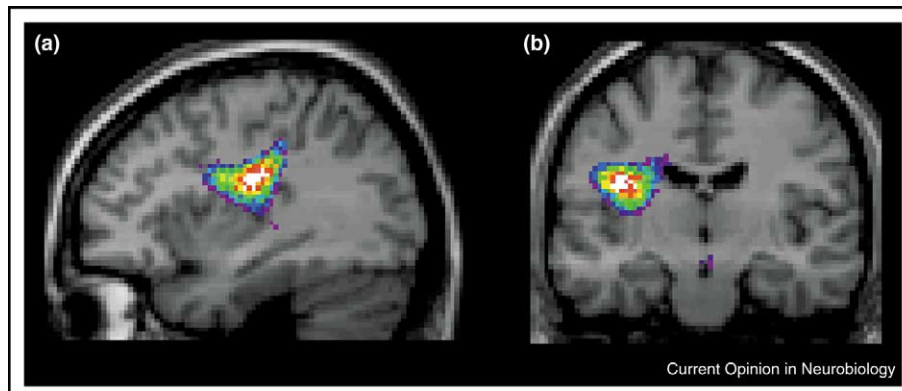
Functional imaging (positron emission tomography) of activation of interoceptive cortex directly correlated with graded cooling of the hands in humans. The focus of activity in the dorsal posterior insular cortex is localized in the sagittal plane in **(a)** and in the coronal plane in **(b)**. These data were obtained in the first identification of interoceptive cortex in humans. Adapted from [41].

[1••,26,30]. In non-primates, in contrast, the ACC (i.e. limbic motor cortex) receives integrated homeostatic information from the PB by way of the medial thalamus [13], and lamina I activity is relayed instead to ventrolateral orbitofrontal cortex through the submedial nucleus [1••]. Physiological and behavioral studies validate the primordial role of the ACC in homeostatic behavior in rats [16•] and in the affective/motivational component of human pain by way of the direct lamina I path to MDvc [1••,2,39,40].

Homeostatic emotions
The direct activation of both the interoceptive cortex and the ACC by the distinct homeostatic modalities corresponds with the simultaneous generation of both a sensation and a motivation. Thus, these feelings constitute emotions that reflect the survival needs of the body. Pain, temperature, and itch are homeostatic emotions that drive behavior, just as hunger and thirst are [2].

Consistent with this view, the functional imaging data we acquired that differentiated cortical activity correlated with subjective ratings of cooling stimuli in humans (in contrast to the representation of objective temperature in interoceptive cortex) [41] indicated that a re-representation of interoceptive cortical activity in the right anterior insula is associated with subjective feelings. This same site is activated in virtually every imaging study of human emotions, and so it seems to provide an image of the physical self as a feeling (sentient) entity, which is a characteristic of human consciousness [1••]. The conclusion that the subjective image of the 'material me' is formed on the basis of the sense of the homeostatic condition of each individual's body is consistent with the ideas of James [42] and Damasio [43], and with recent imaging studies that correlate homeostatic processing with emotional awareness [44,45•]. The association of this

site with the subjective perception of pain [46•], the anticipation of pain [47,48], the subjective reduction of pain (placebo analgesia) [49••], and the subjective generation of pain (hypnotic psychogenic pain) [50] underscores the importance of this meta-representation of interoceptive state for clinical progress on the effects of emotion and belief on health. Furthermore, the recognition that sensual touch is incorporated in the interoceptive system emphasizes the need to understand the neurobiological basis of the importance of conspecific human contact for emotional and physical health [1••,34•].

Conclusions
Recent findings have identified a homeostatic afferent path that represents the physiological condition of all tissues of the body. The direct 'encephalized' inputs in humans provide the substrate for homeostatic emotions involving distinct sensations, engendered in interoceptive and anterior insular cortex (the feeling self), as well as affective motivations, engendered in the ACC (the behavioral agent). These findings explain the distinct nature of pain, temperature, itch, sensual touch and other bodily feelings from cutaneous mechanoreception (somatosensory touch) and they identify the long-missing peripheral and central afferent complement to the efferent autonomic nervous system. These findings reveal a cortical interoceptive image that differentiates primates from non-primates neuroanatomically, and a representation of the feeling self that seems to differentiate humans from non-human primates.

The subjective differences that distinguish the well-discriminated feelings that arise from skin, muscle and joints from the more diffuse feelings associated with the viscera once led to the long-standing narrow view of interoception. These differences may reflect opponent processing between parasympathetic and sympathetic afferents, in parallel with their opponent efferent actions [1••,11].

Many observations indicate that such mutually inhibitory afferent interactions are essential for cardiorespiratory and visceromotor control. Opponent lateralization in the insula has been observed for several visceral functions. This issue deserves intense study because of the potential clinical significance.

Finally, these findings suggest that endogenous homeostatic control mechanisms modulate the integration of afferent activity that produces the feelings from the body, which underscores the crucial dependence of subjective well-being on the physiological health of the body. The emerging evidence from imaging studies that volitional cortical control in humans can directly modify homeostatic integration and the substrate of the feeling self [44,45•,49••,50] signifies the fundamental role of this interoceptive system in human consciousness.

Update

Since this review was submitted several interesting and relevant studies have been published in this area. New imaging results relevant to interoception and the feeling self are rapidly accumulating, such as the fMRI study from Bingel *et al.* [51•] confirming that laser-evoked pain distinguishes activation of interoceptive cortex from the neighboring somatosensory cortex. Critchley *et al.* [52] contribute a review of the imaging literature on emotion in which the concepts of interoception and the role of the anterior insula in subjective emotion have not been incorporated yet, which clearly illuminates the explanatory power of these concepts. Damasio [53], the author of the 'somatic marker' hypothesis of consciousness (the idea that self-awareness emerges from an image of the homeostatic state of the body), presents an opinion essay on the neural basis of the self that highlights the fundamental role of the interoceptive pathway leading to the right insula. Cameron and Minoshima [54] present an imaging study of the sensations elicited by intravenous adrenalin, a classic mode of activating interoceptive feelings of an aroused internal state. Phillips *et al.* [55•] show that there is a strong correlation between activation of the right anterior insula and ACC and the increased emotional anxiety produced by non-noxious visceral distension while viewing fearful faces.

Acknowledgements

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Craig AD: **How do you feel? Interoception: the sense of the**
•• **physiological condition of the body**. *Nat Rev Neurosci* 2002,
   3:655-666.
This review presents a detailed description of the concept summarized in the present article.

2. Craig AD: **Pain mechanisms: labeled lines versus convergence in central processing**. *Annu Rev Neurosci* 2003, **26**:1-30.

3. Cannon WB: *The Wisdom of the Body*. New York: Norton & Company; 1939.

4. Panneton WM: **Primary afferent projections from the upper respiratory tract in the muskrat**. *J Comp Neurol* 1991, **308**:51-65.

5. Altman J, Bayer SA: **The development of the rat spinal cord**. *Adv Anat Embryol Cell Biol* 1984, **85**:1-164.

6. Craig AD: **Propriospinal input to thoracolumbar sympathetic nuclei from cervical and lumbar lamina I neurons in the cat and the monkey**. *J Comp Neurol* 1993, **331**:517-530.

7. Holstege G: **Direct and indirect pathways to lamina I in the medulla oblongata and spinal cord of the cat.** In *Progress in Brain Research* Volume 77. Edited by Fields HL, Besson, JM. Amsterdam: Elsevier; 1988:47-94.

8. Sato A, Schmidt RF: **Somatosympathetic reflexes: afferent fibers, central pathways, discharge characteristics**. *Physiol Rev* 1973, **53**:916-947.

9. Craig AD: **Distribution of brainstem projections from spinal lamina I neurons in the cat and the monkey**. *J Comp Neurol* 1995, **361**:225-248.

10. Pan B, Castro-Lopes JM, Coimbra A: **Central afferent pathways conveying nociceptive input to the hypothalamic paraventricular nucleus as revealed by a combination of retrograde labeling and c-*fos* activation**. *J Comp Neurol* 1999, **413**:129-145.

11. Saper CB: **The central autonomic nervous system: conscious visceral perception and autonomic pattern generation**. *Annu Rev Neurosci* 2002, **25**:433-469.

12. Swanson LW: **Cerebral hemisphere regulation of motivated behavior**. *Brain Res* 2000, **886**:113-164.

13. Krout KE, Loewy AD: **Parabrachial nucleus projections to midline and intralaminar thalamic nuclei of the rat**. *J Comp Neurol* 2000, **428**:475-494.

14. Zhang ZH, Oppenheimer SM: **Baroreceptive and somatosensory convergent thalamic neurons project to the posterior insular cortex in the rat**. *Brain Res* 2000, **861**:241-256.

15. Yasui Y, Breder CD, Saper CB, Cechetto DF: **Autonomic responses and efferent pathways from the insular cortex in the rat**. *J Comp Neurol* 1991, **303**:355-374.

16. Johansen JP, Fields HL, Manning BH: **The affective component**
•   **of pain in rodents: direct evidence for a contribution of the anterior cingulate cortex**. *Proc Natl Acad Sci USA* 2001, **98**:8077-8082.
This study confirms the primordial role of the ACC in aversive conditioning. Such lesions should similarly block other homeostatic behavioral motivations, such as thermoregulatory behavior in non-primates, and perhaps the unpleasant nature of pain in humans.

17. Darwin C: *The Expression of the Emotions in Man and Animals*. Chicago: University of Chicago Press (1965 reprint); 1872.

18. Adreani CM, Kaufman MP: **Effect of arterial occlusion on responses of group III and IV afferents to dynamic exercise**. *J Appl Physiol* 1998, **84**:1827-1833.

19. Vallbo ÅB, Olausson H, Wessberg J: **Unmyelinated afferents constitute a second system coding tactile stimuli of the human hairy skin**. *J Neurophysiol* 1999, **81**:2753-2763.

20. Light AR: *The Initial Processing of Pain and Its Descending Control: Spinal and Trigeminal Systems*. Basel: Karger; 1992.

21. Andrew D, Craig AD: **Spinothalamic lamina I neurons selectively**
•   **sensitive to histamine: a central neural pathway for itch**. *Nat Neurosci* 2001, **4**:72-77.
This study confirms that lamina I includes several distinct sensory channels associated with the condition of the body by identifying a specific substrate for the sensation of itch.

22. Wilson LB, Andrew D, Craig AD: **Activation of spinobulbar lamina**
•   **I neurons by static muscle contraction**. *J Neurophysiol* 2002,
    87:1641-1645.
This study identifies lamina I neurons selectively responsive to small-
diameter muscle afferent input that provide a substrate for homeostatic
(cardiovascular) adjustments to exercise.

23. Andrew D, Craig AD: **Responses of spinothalamic lamina I
    neurons to maintained noxious mechanical stimulation in the
    cat**. *J Neurophysiol* 2002, **87**:1889-1901.

24. Craig AD, Andrew D: **Responses of spinothalamic lamina I
    neurons to repeated brief contact heat stimulation in the cat**.
    J Neurophysiol 2002, **87**:1902-1914.

25. Diesel DA, Tucker A, Robertshaw D: **Cold-induced changes in
    breathing pattern as a strategy to reduce respiratory heat loss**.
    J Appl Physiol 1990, **69**:1946-1952.

26. Craig AD, Bushnell MC, Zhang E-T, Blomqvist A: **A thalamic
    nucleus specific for pain and temperature sensation**.
    Nature 1994, **372**:770-773.

27. Craig AD, Zhang ET, Blomqvist A: **Association of spinothalamic
    lamina I neurons and their ascending axons with calbindin-
    immunoreactivity in monkey and human**. *Pain* 2002,
    97:105-115.

28. Beckstead RM, Morse JR, Norgren R: **The nucleus of the solitary
    tract in the monkey: projections to the thalamus and brain stem
    nuclei**. *J Comp Neurol* 1980, **190**:259-282.

29. Blomqvist A, Zhang ET, Craig AD: **Cytoarchitectonic and
    immunohistochemical characterization of a specific pain and
    temperature relay, the posterior portion of the ventral medial
    nucleus, in the human thalamus**. *Brain* 2000, **123**:601-619.

30. Craig AD: **Supraspinal projections of lamina I neurons.** In
    Forebrain Areas Involved in Pain Processing. Edited by Besson J-M,
    Guilbaud GOH. Paris: John Libbey; 1995:13-26.

31. Craig AD: **New and old thoughts on the mechanisms of spinal
    cord injury pain.** In *Spinal Cord Injury Pain: Assessment,
    Mechanisms, Management*. Edited by Yezierski RP, Burchiel KJ.
    Seattle: IASP Press; 2002:237-264.

32. Williamson JW, McColl R, Mathews D, Mitchell JH, Raven PB,
•   Morgan WP: **Hypnotic manipulation of effort sense during
    dynamic exercise: cardiovascular responses and brain
    activation**. *J Appl Physiol* 2001, **90**:1392-1399.
This is the latest in a series of imaging studies of exercise, which shows
lateralized modulation of interoceptive cortical activity, cardiovascular
parameters, and perceived exertion by contrasting hypnotic suggestions
of uphill and downhill bicycling.

33. Henderson LA, Macey PM, Macey KE, Frysinger RC, Woo MA,
    Harper RK, Alger JR, Yan-Go FL, Harper RM: **Brain responses
    associated with the valsalva maneuver revealed by functional
    magnetic resonance imaging**. *J Neurophysiol* 2002, **88**:3477-3486.

34. Olausson H, Lamarre Y, Backlund H, Morin C, Wallin BG, Starck G,
•   Ekholm S, Strigo I, Worsley K, Vallbo AB, Bushnell MC:
    **Unmyelinated tactile afferents signal touch and project to
    insular cortex**. *Nat Neurosci* 2002, **5**:900-904.
This fMRI study describes a unique patient with large-fiber polyneuro-
pathy in whom light touch produces an indistinct pleasant sensation and
activation of interoceptive cortex that is distinct from the activation
pattern caused by large-fiber (exteroceptive) mechanoreceptors.

35. Sanchez MM, Young LJ, Plotsky PM, Insel TR: **Autoradiographic
    and *in situ* hybridization localization of corticotropin-releasing
    factor 1 and 2 receptors in nonhuman primate brain**. *J Comp
    Neurol* 1999, **408**:365-377.

36. Greenspan JD, Lee RR, Lenz FA: **Pain sensitivity alterations as a
    function of lesion location in the parasylvian cortex**. *Pain* 1999,
    81:273-282.

37. Opsommer E, Weiss T, Plaghki L, Miltner WHR: **Dipole analysis of
    ultralate (C-fibres) evoked potentials after laser stimulation of
    tiny cutaneous surface areas in humans**. *Neurosci Lett* 2001,
    298:41-44.

38. Augustine JR: **Circuitry and functional aspects of the insular
    lobe in primates including humans**. *Brain Res Rev* 1996,
    22:229-244.

39. Hutchison WD, Davis KD, Lozano AM, Tasker RR, Dostrovsky JO:
    Pain-related neurons in the human cingulate cortex.
    Nat Neurosci 1999, **2**:403-405.

40. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC:
    **Pain affect encoded in human anterior cingulate but not
    somatosensory cortex**. *Science* 1997, **277**:968-971.

41. Craig AD, Chen K, Bandy D, Reiman EM: **Thermosensory
    activation of insular cortex**. *Nat Neurosci* 2000, **3**:184-190.

42. James W: **The Principles of Psychology.** URL:
    http://www.emory.edu/EDUCATION/mfp/james.html#principles

43. Damasio AR: *Descartes' Error: Emotion, Reason, and the Human
    Brain*. New York: Putnam; 1993.

44. Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL,
    Parvizi J, Hichwa RD: **Subcortical and cortical brain activity
    during the feeling of self-generated emotions**. *Nat Neurosci*
    2000, **3**:1049-1056.

45. Critchley HD, Melmed RN, Featherstone E, Mathias CJ, Dolan RJ:
•   **Volitional control of autonomic arousal: a functional magnetic
    resonance study**. *Neuroimage* 2002, **16**:909-919.
This is the latest in a series of fMRI studies showing activity in interoceptive
and homeostatic regions (including the cingulate and the insula) correlated
with autonomic measures in patients and normal subjects, in this case by
using manipulation of biofeedback during a relaxation exercise.

46. Brooks JC, Nurmikko TJ, Bimson WE, Singh KD, Roberts N: **fMRI
•   of thermal pain: effects of stimulus laterality and attention**.
    Neuroimage 2002, **15**:293-301.
This fMRI study shows for the first time that activation of the interoceptive
cortex by noxious heat leads to strong activation of the right anterior
insula if the subject pays attention to the painful stimulus.

47. Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM,
    Rawlins JNP: **Dissociating pain from its anticipation in the
    human brain**. *Science* 1999, **284**:1979-1981.

48. Sawamoto N, Honda M, Okada T, Hanakawa T, Kanda M,
    Fukuyama H, Konishi J, Shibasaki H: **Expectation of pain
    enhances responses to nonpainful somatosensory stimulation
    in the anterior cingulate cortex and parietal operculum/
    posterior insula: an event-related functional magnetic
    resonance imaging study**. *J Neurosci* 2000, **20**:7438-7445.

49. Petrovic P, Kalso E, Petersson KM, Ingvar M: **Placebo and opioid
•• analgesia–imaging a shared neuronal network**. *Science* 2002,
    295:1737-1740.
This study, along with that of Ploghaus *et al.* and Sawamoto *et al.* [47,48],
demonstrates that psychological manipulation of human expectations
modifies activation of the limbic motor (ACC) and limbic sensory (right
anterior insula) cortices associated with the homeostatic emotion of pain. In
other words, the authors reveal the human brain modulating its own
feelings. Consistent with the concept of a meta-representation of inter-
oceptive state, this study in particular seems to show simultaneous mod-
ulation of the right anterior insula (the feeling self) and the periaqueductal
gray (descending analgesic controls) by the ACC (the behavioral agent).

50. Derbyshire S, Whalley M, Oakley D: **Subjects hallucinating pain in
    the absence of a stimulus activate anterior cingulate, anterior
    insula, prefrontal and parietal cortices**. *J Pain* 2003, **4**:39.

51. Bingel U, Quante M, Knab R, Bromm B, Weiller C, Buchel C: **Single
•   trial fMRI reveals significant contralateral bias in responses to
    laser pain within thalamus and somatosensory cortices**.
    Neuroimage 2003, **18**:740-748.
This new study provides the first clear evidence dissociating laser-evoked
pain activation of interoceptive cortex in the dorsal posterior insula from
the second somatosensory cortex in the adjacent parietal operculum.

52. Critchley H: **Emotion and its disorders**. *Br Med Bull* 2003,
    65:35-47.

53. Damasio A: **Mental self: the person within**. *Nature* 2003, **423**:227.

54. Cameron OG, Minoshima S: **Regional brain activation due to
    pharmacologically induced adrenergic interoceptive
    stimulation in humans**. *Psychosom Med* 2002, **64**:851-861.

55. Phillips ML, Gregory LJ, Cullen S, Cohen S, Ng V, Andrew C,
•   Giampietro V, Bullmore E, Zelaya F *et al.*: **The effect of negative
    emotional context on neural and behavioural responses to
    oesophageal stimulation**. *Brain* 2003, **126**:669-684.