ELSEVIER

Interoception: the sense of the physiological condition of the body

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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.

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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].

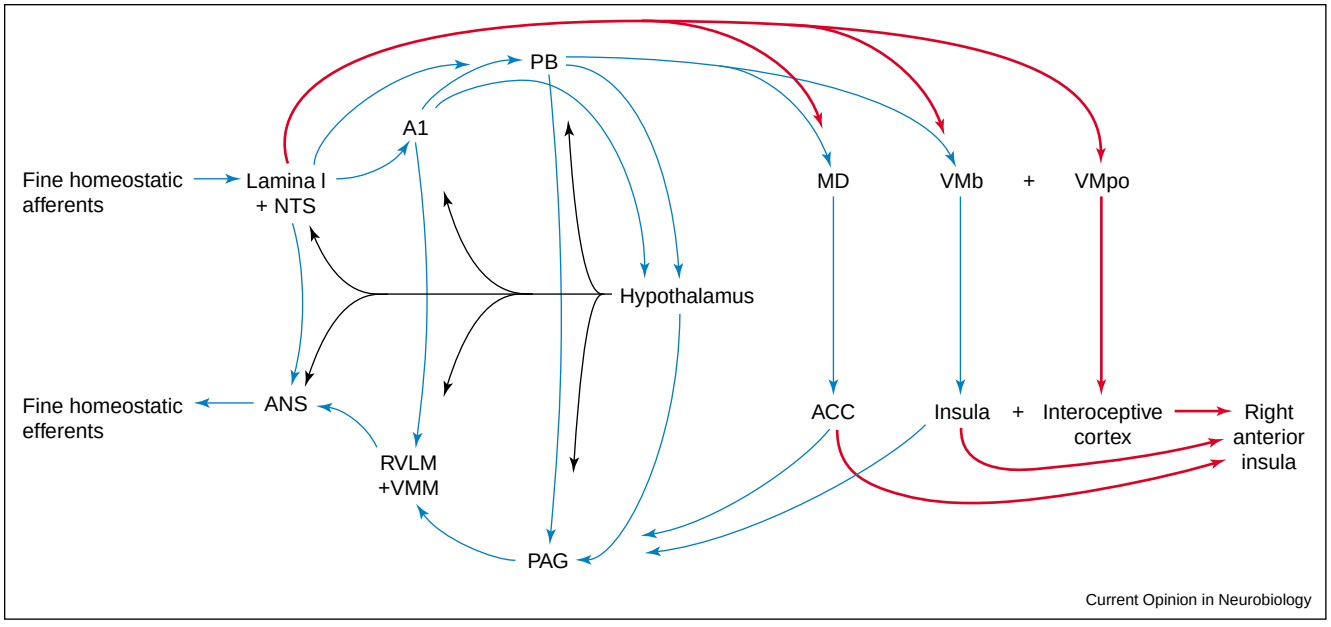
A homeostatic afferent pathway

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 glossopharyngeal) 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 polymodal 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.

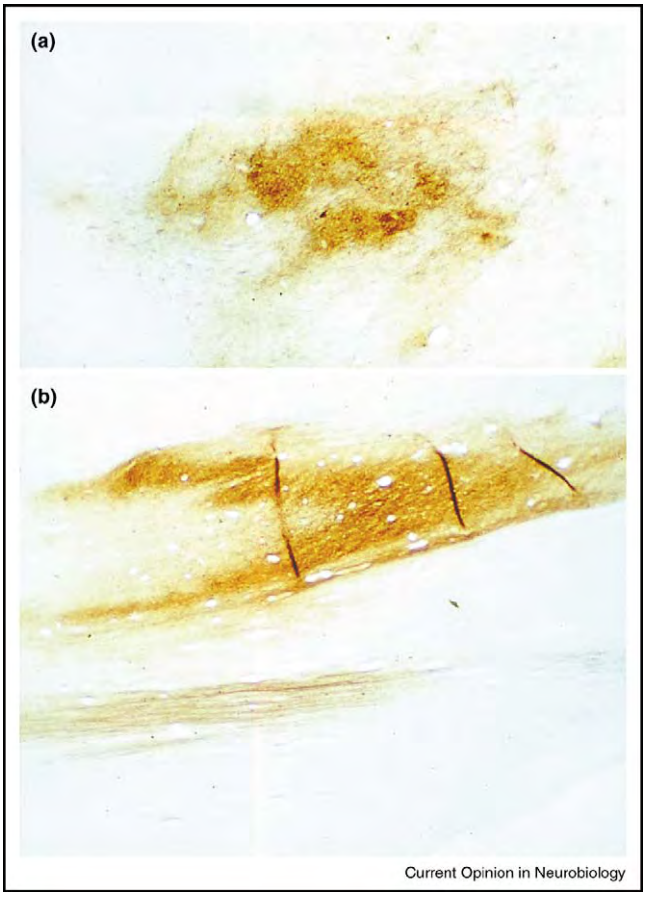
A distinct interoceptive pathway in primates

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 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].

Figure 2

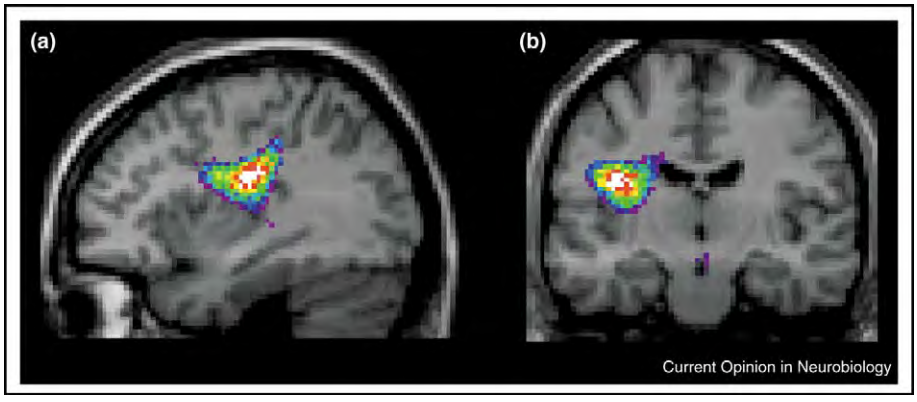


Immunohistochemical identification of the lamina I spinothalamic pathway in humans. Photomicrographs showing **(a)** calbindin-labeled lamina I terminations in the VMpo (coronal section) and **(b)** their ascending axons in the lateral spinothalamic tract (oblique transverse section) in humans. Note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

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.

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