A new view of pain as a homeostatic emotion

A.D. (Bud) Craig

Atkinson Pain Research Laboratory, Barrow Neurological Institute, 350 West Thomas Road, Phoenix, AZ 85013, USA

Pain is conventionally viewed as a pattern of convergent activity within the somatosensory system that represents the exteroceptive sense of touch. Accumulating functional, anatomical and imaging findings indicate that pain is generated by specific sensory channels that ascend in a central homeostatic afferent pathway. Phylogenetically new thalamocortical projections in primates provide a sensory image of the physiological condition of the body and, in addition, direct activation of limbic motor cortex. These findings indicate that the human feeling of pain is both a distinct sensation and a motivation – that is, a specific emotion that reflects homeostatic behavioral drive, similar to temperature, itch, hunger and thirst.

Pain is an enigmatic feeling from the body, distinct from the classical senses because it is multifaceted (it is a discriminative sensation, an affective motivation, a potent autonomic drive and a reflexive motor stimulus) and because it is inherently variable. Most reviewers, following the introduction of the gate-control theory in 1965, have regarded pain as a sub-modality of cutaneous sensation, or exteroception [1–3]. In this conventional view, pain is represented centrally by convergent somatosensory activity conveyed by wide-dynamic-range cells in the deep dorsal horn of the spinal cord to a modifiable pattern detector in the somatosensory thalamus and cortices. However, this view is contradicted by the observations that neither damage nor stimulation of somatosensory cortices affects pain, and that clinical stimulation of somatosensory thalamus can alleviate chronic pain. Recent converging evidence compels a new, specific view of pain as a homeostatic emotion, akin to temperature, itch, hunger and thirst [4,5]. In this view, pain emerges in primates as a feeling from the body that is generated by specific sensory pathways, within a direct thalamocortical projection that extends the afferent limb of the hierarchical homeostatic system to the cortical level. That is, pain is both an aspect of interoception (the sense of the physiological condition of the body) and a specific behavioral motivation. This striking conceptual shift incorporates the multiple facets of pain into one concrete framework, and it provides sound explanations for pain as both a specific sensation and a variable emotional state. These new findings are summarized after considering the nature of homeostasis.

Corresponding author: A.D. (Bud) Craig (bcraig@chw.edu).

Homeostasis maintains the body

Homeostasis, as elucidated by Cannon [6], is a dynamic and ongoing process comprising many integrated mechanisms that maintain an optimal balance in the physiological condition of the body, for the purpose of survival. In mammals, these include autonomic, neuroendocrine and behavioral mechanisms. Homeostasis is commonly regarded as maintaining salt, energy, oxygen and water levels, but Cannon recognized that a change in any one condition usually affects several measures and elicits integrated, hierarchically organized homeostatic responses that restore an optimal balance. Changes in the mechanical, thermal and chemical status of the tissues of the body – stimuli that can cause pain – are important first of all for the homeostatic maintenance of the body.

It is particularly instructive to compare the homeostatic function of thermoregulation with pain for two reasons. First, it has long been known that pain and temperature are processed together in the mammalian CNS, even though the basis – their underlying commonality as aspects of homeostasis – has only recently been recognized. Second, like pain, innocuous temperature sensation (e.g. cool or warm) has traditionally been considered a discriminative and exteroceptive capacity: we typically project thermal sensations to the object we are touching or to the environment, even though it is really changes in the temperature of the skin (and the body core) that are reported by thermosensory afferents [7]. Nevertheless, non-painful thermal stimuli inherently produce an affective motivation, a 'feeling' of pleasantness or unpleasantness that depends on physiological context, and they generate reflexive autonomic adjustments. These aspects directly signify the homeostatic role of temperature sensation.

In fact, the regulatory function of thermal sensibility is its primordial role. All animals thermoregulate. Amoeba, gastropods, fish and lizards all rely on metabolic and behavioral thermoregulatory mechanisms. Homeothermic mammals additionally regulate body temperature by modulating autonomic (cardiorespiratory) activity, which differentially controls blood flow to the thermal core and shell (the skin) [8,9]. Yet thermoregulation in mammals, including humans, necessarily still includes behavioral mechanisms; we not only use clothing, build fires and migrate to temperate climes, but also are motivated to respond behaviorally to immediate changes in the temperature of the core or the skin.

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Homeostatic emotions drive behavior

The affect (i.e. pleasantness or unpleasantness) we feel with an innocuous thermal cutaneous stimulus is the perceptual correlate of thermoregulatory motivation. Think of the discomfort you feel in a room that is too warm or too chilly for energy-efficient thermoneutrality: if you remain in that room, the discomfort grows until it becomes an intractable motivation – even though it is not 'painful', you must respond if you are to survive. The homeostatic role of thermosensory affect is elegantly demonstrated by its inversion under the opposing conditions of hyperthermia or hypothermia [10,11]. So, a cool glass feels wonderful if your body is hot, but it feels gnawingly unpleasant if you are chilled. The primordial thermoregulatory drive, and the motivational affect we perceive, is based on the needs of the body and drives appropriate homeostatic behavior. In the same way, eating salt or sugar is pleasant (and, thus, motivated) if the body needs it but is unpleasant if it does not (so-called stimulus-specific satiety [12]). Homeostatic afferents generate both a sensation and an affective motivation with autonomic sequelae – that is, a feeling from the body that motivates behavior.

Pain is a homeostatic emotion

The basic homeostatic 'feelings', or modalities, include temperature, itch, visceral distension, muscle ache, hunger, thirst, 'air hunger' and sensual touch. All of these inherently generate an emotion that drives homeostatic behavior, and pain is no different. Pain normally originates from a physiological condition in the body that automatic (subconscious) homeostatic systems alone cannot rectify, and it comprises a sensation and a behavioral drive with reflexive autonomic adjustments. Pain can be either unpleasant (as usual) or pleasant (as when it relieves an intense itch). The behavioral drive that we call pain usually matches the intensity of the sensory input but it can vary under different conditions, and can become intolerable or, alternatively, disappear, just as hunger or thirst.

This intuitive perspective of pain as an emotion was professed by both Aristotle and Darwin. Pain became confounded with touch in the conventional view by pattern theorists such as Goldscheider, Weddell, Noordenboos, Melzack and Wall [13] in their attempts to explain neuropathic allodynia (pain upon low-threshold cutaneous stimulation) and central pain (ongoing pain subsequent to CNS damage). They incorrectly thought that these conditions implied that pain could not be represented by specific neural components (which had not yet been demonstrated). In addition, they believed that their pattern theory was supported by the interactions of pain with various physiological (i.e. homeostatic) conditions, such as temperature, blood pressure and hormone level, and with psychological factors such as emotional status, attention and level of arousal (as in the case of hunger). By contrast, the new view of pain as a distinct homeostatic emotion, based on recently identified specific substrates (see following discussion), readily incorporates the interactions of pain with homeostatic conditions and with emotional status and, furthermore, it unifies the different conditions that can cause different types of pain from different tissues (i.e. not just skin) under a common homeostatic function – maintenance of the integrity of the body.

Emotions consist of a sensation and a motivation with direct autonomic effects [12,14], and in this new view, pain is one of many distinct homeostatic emotions that directly reflect the condition of the body. Just as all animals thermoregulate, all vertebrates respond similarly to the noxious stimuli that can cause a feeling of pain in humans [15] and so the neural basis for these integrated homeostatic emotional behaviors must be evolutionarily ancient. The data summarized in the following section clearly reveal a primordial homeostatic afferent pathway that represents painful stimuli in distinct sensory channels alongside all other aspects of the condition of the body.

A homeostatic afferent pathway originating in lamina I

The new view of pain as a homeostatic emotion arises directly from functional anatomical findings in cat and monkey, rather than from philosophical considerations. These results have identified specialized central substrates that represent pain, temperature, itch, muscle ache, sensual touch and other bodily feelings as discrete sensations within a common pathway. They indicate that specific activity representing these modalities is conveyed first of all to homeostatic response regions in the spinal cord and the brainstem. In addition, these findings indicate that in primates a forebrain system has evolved from the hierarchical homeostatic system, and that this provides a discrete cortical image of the afferent representation of the physiological condition of the body (which we term interoception), along with direct activation of limbic motor cortex. The interoceptive system is distinct from the exteroceptive system associated with touch and movement, although there is overlap (in area 3a of the sensorimotor cortex) with respect to pain. These data indicate that in humans pain is an emotion that reflects specific primary homeostatic afferent activity. These results are briefly summarized here, and detailed reviews are available elsewhere [4,5,16].

Spinal components

The small-diameter (Aδ and C) primary afferent fibers that report the physiological status of the various tissues of the body (including nociceptors, thermoreceptors, osmoreceptors and metaboreceptors) terminate monosynaptically on projection neurons in lamina I of the spinal dorsal horn (Fig. 1). The development of these afferents is genetically coordinated with that of lamina I neurons (which originate from progenitors of sympathetic interneurons that migrate to the top of the dorsal horn precisely when the small diameter afferents arrive [17]), indicating that they form a cohesive system for homeostatic afferent activity. Small-diameter afferents that innervate visceral organs by way of the cranial parasympathetic nerves terminate similarly in the solitary nucleus.

Homeostatic afferent integration

The spinal and brainstem projections of lamina I neurons provide the central afferent pathway for homeostasis.

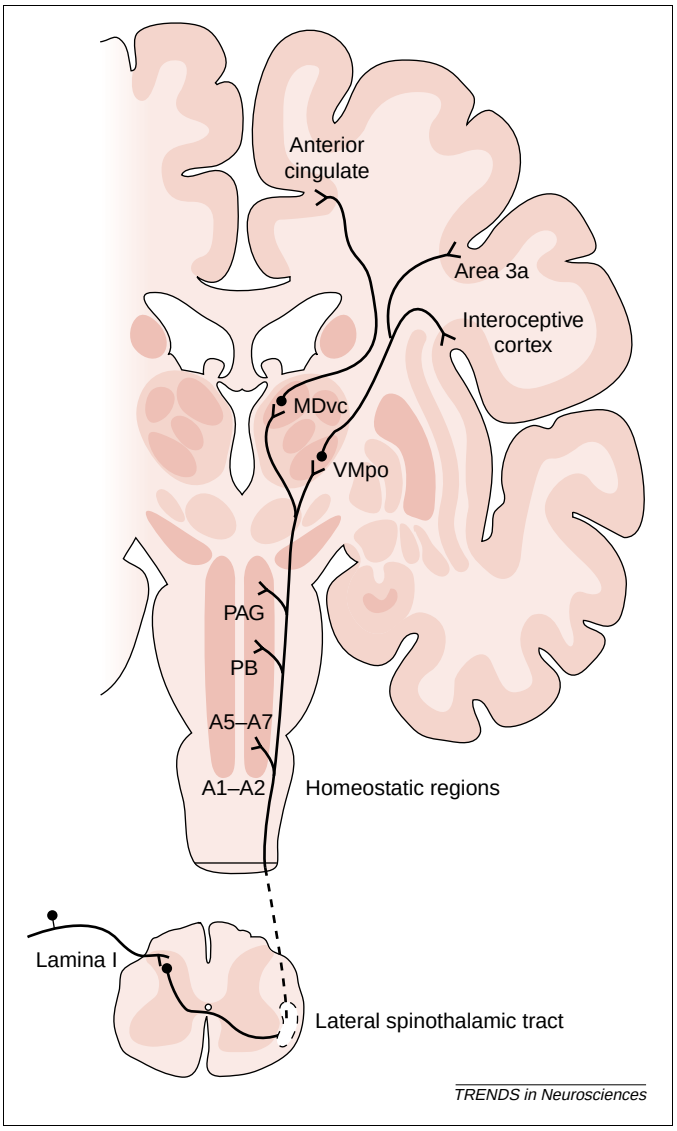

Fig. 1. Summary of the projections of the lamina I system in primates. Modality-specific lamina I neurons project first to autonomic sites in the spinal cord (not shown) and to homeostatic sites in the brainstem [including the noradrenergic cell groups A1–A2 and A5–A7, the parabrachial nucleus (PB) and the periaqueductal gray (PAG)]. In primates, lamina I neurons also project by way of the crossed lateral spinothalamic tract to two sites in the thalamus: the posterior part of the ventral medial nucleus (VMpo) and the ventral caudal part of the medial dorsal nucleus (MDvc). The VMpo provides a high-resolution, modality-specific sensory representation of the physiological condition of the body in interoceptive cortex at the dorsal margin of the insula, and it sends a corollary projection to area 3a in the sensorimotor cortex. The MDvc integrates lamina I input with brainstem homeostatic activity (from PB and PAG) and produces behavioral drive in limbic motor cortex (anterior cingulate). These generate the feeling and the motivation, respectively, that constitute the homeostatic emotion of pain. Reproduced, with permission, from Ref. [5], © (2003) Annual Reviews (www.annualreviews.org).

First, they project strongly to the autonomic cell columns of the thoracolumbar spinal cord, where sympathetic preganglionic motoneurons are located. In the brainstem, they project to major homeostatic integration sites (including the caudal and rostral ventrolateral medulla, catecholamine cell groups A1–A2 and A5–A7, the parabrachial nucleus and the periaqueductal gray) that also receive parasympathetic afferent activity by way of the solitary nucleus and that are heavily interconnected with the hypothalamus and amygdala. These hierarchical spinal and bulbar projections provide the long-missing central afferent limb of the autonomic nervous system and they 'substantialize' (provide the substrate for) the modality-selective somato–autonomic reflexes activated by spinal small-diameter afferents that are crucial for homeostatic function [18]. In turn, lamina I receives descending modulation directly from brainstem pre-autonomic sources, and lamina I is selectively targeted by descending fibers from the hypothalamus. Significantly, these are not only emergency pathways but, rather, are continuously engaged [19,20].

Distinct sensory channels

Spinal and trigeminal lamina I neurons comprise several modality-selective, morphologically distinct classes of neurons that each receive selective input from particular subsets of afferents [5]. These classes correspond with distinct feelings from the body (including first [sharp] pain, second [burning] pain, cool, warm, itch, sensual touch and muscle burn) although, as discussed in the following section, their activity must be integrated in the forebrain. Lamina I neurons that project to the contralateral thalamus ascend in the lateral spinothalamic tract (STT), precisely where cordotomy lesions interrupt these feelings. The distinct role of lamina I STT neurons in sensation is convincingly highlighted by the histamine-responsive cells that correspond uniquely with the sensation of itch [21]. Whereas lamina I is usually related to pain and temperature, its role in homeostasis is clearly revealed by the neurons that respond selectively to small-diameter muscle afferents, which subserve ongoing cardiorespiratory adjustments to muscular work but that, when strongly activated, can signal muscle burn and pain [20].

Direct input to primate forebrain

Ascending lamina I activity is integrated mainly in several brainstem sites in non-primates, but in primates there is a direct thalamocortical homeostatic afferent pathway to the dorsal posterior insular cortex [22–24]. There, a discrete field provides a topographic, modality-selective representation of all interoceptive afferent activity from lamina I (i.e. sympathetic afferent input) and from the solitary nucleus (i.e. parasympathetic afferent input). This pathway is just visible in monkeys but in humans it is greatly enlarged and microstimulation, lesion and functional-imaging studies provide convergent evidence confirming its role in pain, temperature, itch, muscle sensation, sensual touch, hunger, thirst, cardiorespiratory activity, and so on [4,25]. In humans, this interoceptive cortical image engenders discriminative sensations, and it is re-represented in the middle insula and then in the right (non-dominant) anterior insula. This seems to provide a meta-representation of the state of the body that is associated with subjective awareness of the material self as a feeling (sentient) entity – that is, emotional awareness – consistent with the ideas of James and Damasio [4,14,26,27].

The data indicate that innocuous thermosensory activity is uniquely represented in the interoceptive cortex and does not cause correlative activity in parietal somatosensory cortices, and that the same is true for muscle exercise, hunger and thirst [4,28,29]. This validates the neuroanatomical and neurochemical distinctness of interoceptive modalities, which are important for homeostasis and autonomic activity, from the exteroceptive modalities of touch and limb position, which are important for somatic motor control. Further, the primordial role of the insular cortex seems to be modulation of homeostatic integration in the brainstem, where its descending projections terminate [30]. Thus, the 'encephalized' representation of the condition of the body in humans emerged evolutionarily from the afferent limb of the hierarchical homeostatic system. Activity that produces pain in humans ascends in this pathway because its primary role has been homeostasis for millions of years.

The lamina I STT pathway in primates also directly activates the anterior cingulate cortex (ACC) and area 3a, which is intercalated between the primary somatosensory area (S1) and the primary motor area [4]. The ACC projection is directly associated with the affective motivation of pain [31,32]. The area 3a projection could be involved with cortical control of the reflex motor action of pain, consistent with the projection of vagal afferent activity to anterolateral area 3a [33], although a role in perception (e.g. the exteroceptive capacity of cutaneous pain) should still be considered [34]. (Area 3a is the probable source of activation that is often interpreted as 'S1' in imaging studies of pain [5].)

Notably, only primates seem to have the neuroanatomical capacity to feel pain in the same way that humans do. In non-primates, ascending lamina I activity converges in the brainstem (particularly in the parabrachial nucleus) with many other inputs (e.g. vagal, vestibular and retinal [35]) to produce an integrated homeostatic behavioral drive effected by projections to the hypothalamus, midline thalamus (and ACC) and amygdala [36]. Several behavioral findings in rats support the primordial role of lamina I neurons and the ACC in aversive responses to noxious stimuli and neural damage [37–39].

Physiological evidence that burning pain is a homeostatic feeling

One class of nociceptive lamina I STT neurons is associated with first (sharp) pain and another with second (burning) pain. The latter class of neurons has a clear relationship with homeostasis. These polymodal nociceptive neurons receive predominantly monosynaptic C-fiber input and respond to noxious heat, pinch and noxious cold (hence, they are called 'HPC' cells). Their correspondence with burning pain is revealed by their unique ability to explain three phenomena: (1) the uniformly dull, burning sensation evoked by heat, pinch or cold (but not touch) during a pressure block of A-fiber conduction in a peripheral nerve [40]; (2) the ice-like burning sensation unmasked by simultaneous warming and cooling in the thermal grill illusion of pain [4]; and (3) the augmentation and 'reset' of burning pain selectively elicited by repeated brief-contact heat stimuli [41,42]. By stark contrast, the wide-dynamic-range cells of the conventional view of pain cannot explain these phenomena.

The HPC cells are associated with homeostasis by their ongoing activity and by their sensitivity to cold. Their ongoing activity is directly correlated with their afferent C-fiber input [43], consistent with the hypothesis that such activity relates tissue metabolic needs on an ongoing basis. Their sensitivity to cold shows static responsiveness below ~24°C, the thermoneutral (comfortable) ambient temperature [5]. Humans experience increasing discomfort at temperatures below 24°C, but cold does not normally produce pain until ~15°C, where HPC activity accelerates and, significantly, cooling-specific lamina I cell activity plateaus. The inference that cold becomes noxious when HPC activity exceeds innocuous cooling-specific activity is dramatically confirmed by the observation that an artificial reduction in cooling activity (by a peripheral nerve block of cooling-sensitive Aδ fibers or by simultaneous warming in the thermal grill illusion of pain) enables nominally innocuous cool temperatures (up to 24°C) to produce burning pain.

These findings indicate that the perception of burning pain (i.e. unpleasantness or thermal distress) depends on the forebrain integration of these two sensory channels, as well as on core temperature [11,31], directly implying that it is a homeostatic motivation. This physiological evidence confirms the anatomical finding that homeostasis, rather than the heuristic simplification 'nociception', is the fundamental role of the small-diameter afferent fiber and lamina I system and is the essential nature of pain [5].

Concluding remarks

These findings indicate that pain in humans is a homeostatic emotion reflecting an adverse condition in the body that requires a behavioral response. It involves a distinct sensation, engendered in interoceptive and anterior insular cortex (the feeling self), and an affective motivation, engendered in the ACC (the behavioral agent). It generates reflexive autonomic responses and motor responses that are under cortical control. The new findings provide specific substrates for each of these aspects within a common framework of homeostasis.

This new view differs fundamentally from the prior conventional view in several ways. It incorporates specific sensory channels for different kinds of pain and for pain of different tissue origins. It provides a fast (sharp) pain channel that can elicit fight-or-flight behavior [43,44] and a slow (burning) pain channel that can engage long-term responses, sickness behavior and immune function [42,45]. The discriminative, topographic representations in interoceptive cortex obviate the involvement of S1 in feelings from the body [5]. Viewing pain as a homeostatic emotion readily incorporates the interactions of pain with other homeostatic functions and with emotional state, such as in psychosomatic illness. Sensitization of lamina I STT nociceptive neurons can easily explain neuropathic allodynia [5,37], and loss of the inhibition imposed on the

motivational pathway by thermosensory activity provides a concrete anatomical model for central pain [4]. This view also provides a clear explanation for the conjoint activation of the ACC and the right anterior insula in placebo analgesia [4,46].

This perspective suggests new directions for research that could have strong impact on clinical therapy. For example, other homeostatic variables, such as salt and water balance, could have direct impact on the integrated activity that underlies the motivation called 'pain', as in the mysterious fibromyalgia syndrome [47]. Understanding the mechanisms underlying the augmentation of activity in the polymodal nociceptive channel could be particularly fruitful for identifying new therapies for chronic pain. Lastly, it remains to be seen how endogenous homeostatic control mechanisms provide integrated modulation of the afferent activity that produces the emotion of pain, and how these might best be engaged by clinical intervention.

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