INTEROCEPTION AND THE SENTIENT SELF

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INTRODUCTION

Langley was the first person to describe the autonomic nervous system (ANS) (*Langley*, 1903). Near the end of his report, he noted explicitly that he had omitted a description of the sensory inputs that are required for the ANS to function efficiently; he explained that he had not been able to unequivocally distinguish the necessary elements anatomically. As Cannon later emphasized, the neural processes (autonomic, neuroendocrine and behavioural) that maintain an energy-efficient, physiological balance across conditions in the body, i.e., homeostasis, must receive modality-selective afferent inputs that report the condition of the tissues of the body (*Cannon*, 1939). Finally, Prechtl and Powley suggested that the missing category of homeostatic afferents could be identical to the anatomically well-defined small, dark B-cells in the mammalian dorsal root ganglia (*Prechtl* and *Powley*, 1990); unfortunately, their proposal was rejected by nearly all of the discussants of their publication. Had they been aware of the findings described in the present report, they would have recognized the central continuation of the pathway they had envisioned and the unmistakable confirmation of their proposal.

The sensory pathway that is described in the following sections provides not only the sensory inputs required for organotopic homeostatic control of the body's condition, but also the basis for human feelings from the body, such as cool, warm, pricking pain, burning pain, itch, sensual touch, muscle ache, bowel distension, urge to urinate, vascular flush, hunger, taste, thirst and "air hunger". These feelings, which are all related to the condition of the body and underlie mood and emotional state, are all associated with strong affective motivations that are the correlates of behavioural responses needed to maintain the health of the body. Thus, these feelings can all be viewed as homeostatic emotions, a concept which emphasizes their essential autonomic role. The anatomical pathways described below underpin the homeostatic nature of these feelings, and conversely, reveal a fundamental relationship with the ANS that explains why the affectively charged feelings from the body all have strong autonomic sequelae. So, pain is accompanied by autonomic changes because it is the perceptual correlate of a behavioural motivation generated in response to a condition which the homeostatic system cannot rectify automatically.

In the conventional view, the well-discriminated feelings of temperature, itch and pain are associated with a somatosensory system that maps the sense of touch to a recognized map of the body (homunculus) in Rolandic cortex (Figure 1). In contrast, the less distinct visceral feelings of vasomotor activity, hunger, thirst and internal sensations are said to be associated with a separate visceral system in more archaic regions. That conceptualization obscures fundamental discrepancies, such as the fact that stimulation of Rolandic somatosensory cortices almost
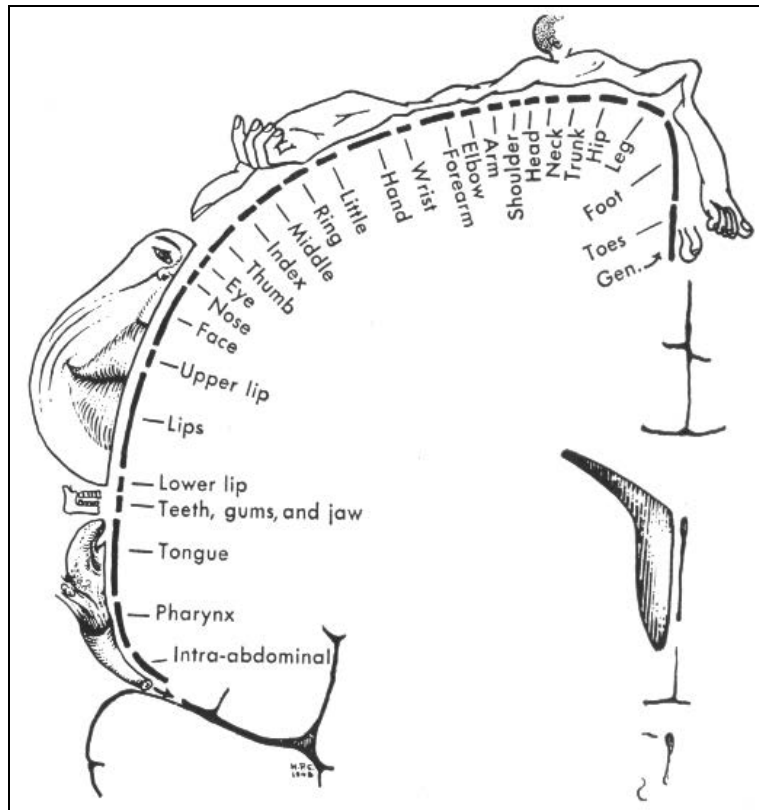
Figure 1: Human homunculus (*Penfield* and *Rasmussen*, 1950).

never produces feelings of pain or temperature, or that lesions of Rolandic cortex have no effect on temperature or pain sensations. It also leaves unexplained the inherent emotional (affective/motivational) qualities and reflexive autonomic effects that all feelings from the body share, which distinguish them from tactile mechanoreception and from the sense of limb position (proprioception). In the following sections it is shown that all feelings from the body are represented in a phylogenetically new system in primates that evolved from the afferent limb of the evolutionarily ancient, hierarchical homeostatic system that maintains the integrity of the body, that is, the sensory complement of the ANS. These feelings thus represent a sense of the physiological condition of the entire body, providing a broad redefinition of the term 'interoception'. More importantly, from the clinical perspective, these findings reveal that feelings from the body, such as pain, are inherently linked with autonomic conditions, such as plasma extravasation or cardiac rhythmicity, because they are, respectively, sensory and motor aspects of the same homeostatic system. In humans, further processing builds a meta-representation of primary interoceptive activity, engendered in the 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. More detailed reviews of the evidence for these views are available elsewhere (*Craig*, 2002, 2003a, 2009).
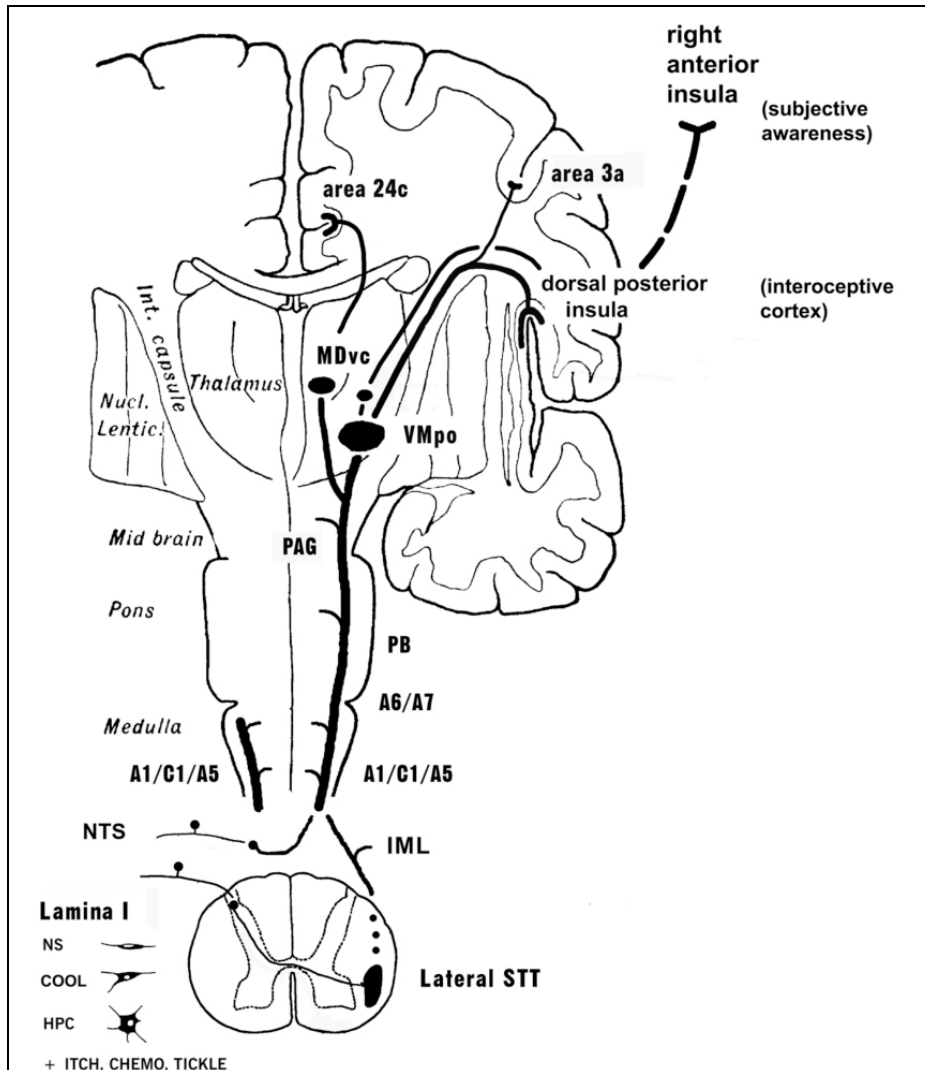
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Figure 2: The overall organization of lamina I projections in the primate.

THE ASCENDING PATHWAY AND ITS PRINCIPLES OF ORGANIZATION

Spinal cord

In the periphery, the small-diameter A-delta and C primary afferent fibres that emerge late in development from small dorsal root ganglion cells (small, dark B-cells) innervate every tissue of the body, and they project to the superficial dorsal horn of the spinal cord or to the medullary nucleus of the solitary tract (NTS). The output neurons from these two regions (i.e., lamina I and the NTS) project to the homeostatic integration sites and pre-autonomic motor regions in the brainstem. Lamina I neurons also project heavily to the spinal autonomic nuclei, where sympathetic

pre-ganglionic neurons are found. Altogether, these substrates provide the sensory and motor components of the hierarchically organized homeostatic (autonomic) nervous system. This conclusion is underscored by the observation that the descending projections from the hypothalamus (which many view as a master autonomic control centre) target exactly these sites. Indeed, the superficial dorsal horn that is part of the homeostatic afferent system is easily distinguishable in myelin-stained transverse sections of the human spinal cord from the deep dorsal horn, where large neurons receive input from large-diameter primary afferents (which emerge early in development from large dorsal root ganglion cells, or A-cells) and project to motorneurons in the ventral horn and to motor control sites centrally. Thus, the terms interoception and exteroception can be redefined (*Craig*, 2002) to differentiate these two systems (i.e., one that controls smooth muscle, as distinct from one that receives large-diameter mechanoreceptive and proprioceptive inputs and controls striate muscle). An important principle of the hierarchical homeostatic system is that it has identifiable sensory and motor components at each level that are tightly interconnected centrally.

Brainstem

Lamina I and NTS neurons 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 2) and generating spino-bulbospinal loops for somato-autonomic reflexes (*Sato* and *Schmidt*, 1973; *Craig*, 1995). In all mammals, the highest level of this homeostatic hierarchy in the upper brainstem consists of the parabrachial nuclei (PB) and the periaqueductal gray (PAG). These sites can

be viewed as the lowest level of the so-called limbic system that controls emotional behaviour (*Heimer* and *Van Hoesen*, 2006), because together they organize whole-body behaviours that serve life-supporting functions (cardiorespiratory control, ingestion, elimination, reproduction, etc.), as discovered in studies of chronic decerebrate and decorticate animals at the end of the 1800's (e.g., *Sherrington*, 1900).

More recent experiments that revealed approach/avoidance columns in the PAG with correlative, opposing cardiorespiratory actions (*Bandler* et al., 1991) supply the fundamental pattern for a combined behavioural and autonomic opponent organization that many authors have envisaged in the forebrain of mammals and all vertebrates (*Solomon*, 1980; *Craig*, 2005; *Uvnas-Moberg*, 2005; *Macneilage* et al., 2009). The principle of opponent organization is found throughout physiology, e.g., in colour vision, antagonist muscles, hormones controlling water balance, and cardiac function, probably because it provides an energy-efficient method for precise control. Indeed, opponent interaction is present between the lamina I (i.e., "sympathetic") afferent pathway and the NTS (i.e., vagal, or "parasympathetic") afferent pathway already in the medulla and spinal cord (*Chandler* et al., 2002; *Potts*, 2006), and a similar behavioural/autonomic opponent organization is present in the medial and lateral portions of the hypothalamus (*Swanson*, 2000). Thus, the PB and PAG can be viewed as identifiable, complementary sensory and motor regions, respectively, that support homeostasis with a coordinate behavioural/autonomic opponent organization.

Forebrain

In mammals other than primates, the ascending pathway from lamina I

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and the NTS generates widely scattered projections, and the main homeostatic afferent pathway to their forebrains conveys integrated activity from PB to hypothalamus, amygdala, and, by way of the thalamus, to striatum and insular and cingulate cortices (*Saper*, 2002). Accordingly, multimodal context-dependent responses have been recorded in these regions in the rat. The insular cortex can be viewed as limbic sensory cortex, because it provides descending control of brainstem homeostatic integration in PB, and the cingulate cortex can be viewed as limbic motor cortex, because it projects densely to the behavioural/autonomic columns of the PAG. Lesions at cingulate cortex and PAG disrupt homeostatic behaviour in rodents (*Johansen* et al., 2001; *Saper*, 2002). The emotional behaviour of non-primate mammals suggests the anthropomorphic inference that they experience feelings from the body in the same way that humans do. However, the neuro-anatomical evidence indicates that they cannot, because the phylogenetically new pathway that underlies feelings from the body in humans is either rudimentary or absent in non-primates (*Craig*, 2002).

In primates, lamina I neurons and NTS neurons extend such pathways by projecting topographically to a pair of relay nuclei in the postero-lateral thalamus, the posterior ventral medial nucleus (VMpo) and the adjoined basal ventral medial nucleus (VMb). The lamina I axons ascend in the lateral spinothalamic tract, precisely where lesions can selectively interrupt the feelings from the body in human patients (*Craig* et al., 2002). The VMpo / VMb is organized antero-posteriorly, orthogonal to the medio-lateral topography of the main somatosensory ventral posterior (VP) nuclei, to which it is connected at the representation of the mouth. The VMb receives direct input from NTS in addition to the integrated input that it receives from PB in all mammals (*Beckstead* et al., 1980). The VMpo is small in macaque monkeys, but in the human thalamus it is almost half as large as the VP (*Blomqvist* et al., 2000).

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). The projections of VMpo and VMb extend over the entire posterior-to-anterior extent of the insula in the macaque monkey (*Beckstead* et al., 1980; *Craig* and *Zhang*, 2005; *Ito* and *Craig*, 2008), approximately 6-8 mm. However, in humans, the insula extends approx. 50-60 mm antero-posteriorly, and functional imaging studies indicate that lamina I input (e.g., pain, temperature, or itch stimuli) first activates the most posterior 15-20 mm, while vagal and gustatory input (e.g., gastric distension, salty intensity) activates the next 10 mm or so (*Craig*, 2009, 2010; *Small*, 2010). In other words, primary interoceptive cortex occupies the entire dorsal insula in monkeys, but only the posterior third in humans. This pathway contains modality-selective components that each generate a distinct "feeling" from the body in humans, including first (pricking) pain, second (burning) pain, cool, warm, itch, muscle ache, gastric distension, vasomotor flush, sweet, salty, and so on. PET imaging studies of innocuous cool sensation (*Craig* et al., 2000) showed that activation in the dorsal posterior insula, which is linearly related to objective stimulus intensity, is accompanied by activation of the mid-insula and the anterior insula, where activity correlates much more strongly with subjective feelings of cool. Indeed, activation in the anterior insula is
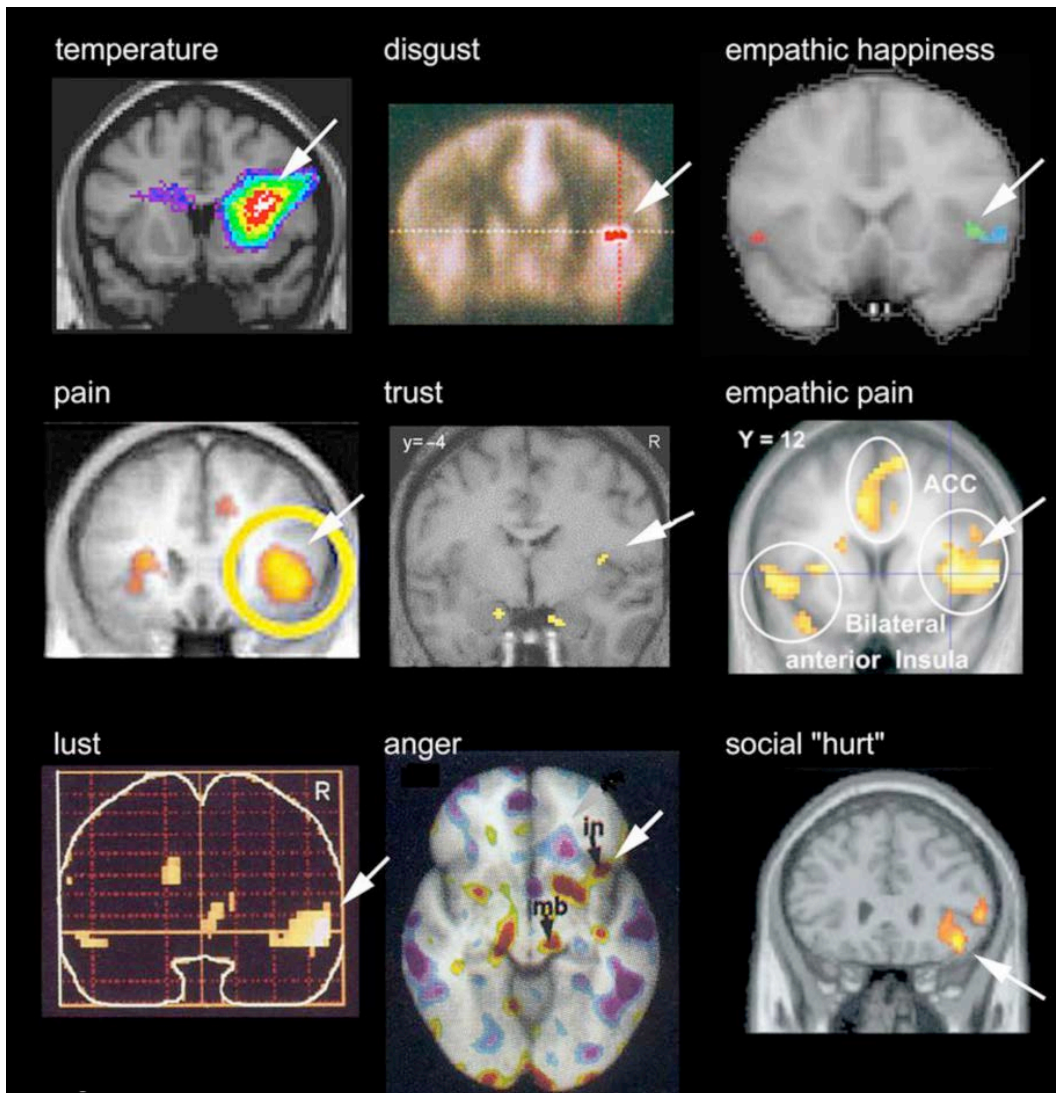
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Figure 3: Activation of the right anterior insula by subjective feelings (*Craig*, 2002).

uniquely associated with subjective feelings of all kinds (Figure 3) (*Craig*, 2002, 2009). This pattern suggests a posterior-to-anterior processing gradient in the human insular cortex, which fits with considerable evidence (e.g. *Schweinhardt* et al., 2006) and that subjective feelings are based directly on homeostatic sensory integration, which is consistent with the James-Lange theory of emotion and the "somatic marker" hypothesis (*James*, 1890; *Damasio*, 1993). This pattern also suggests that integration within the insula generates the template for a "feeling", namely a neural representation of homeostatic sensori-motor conditions that can valuate or quantify energy utilization, thus providing a metric for amodal computation of homeostatic efficiency (a "common currency") (*Rainville* et al., 2006; *Duncan* and
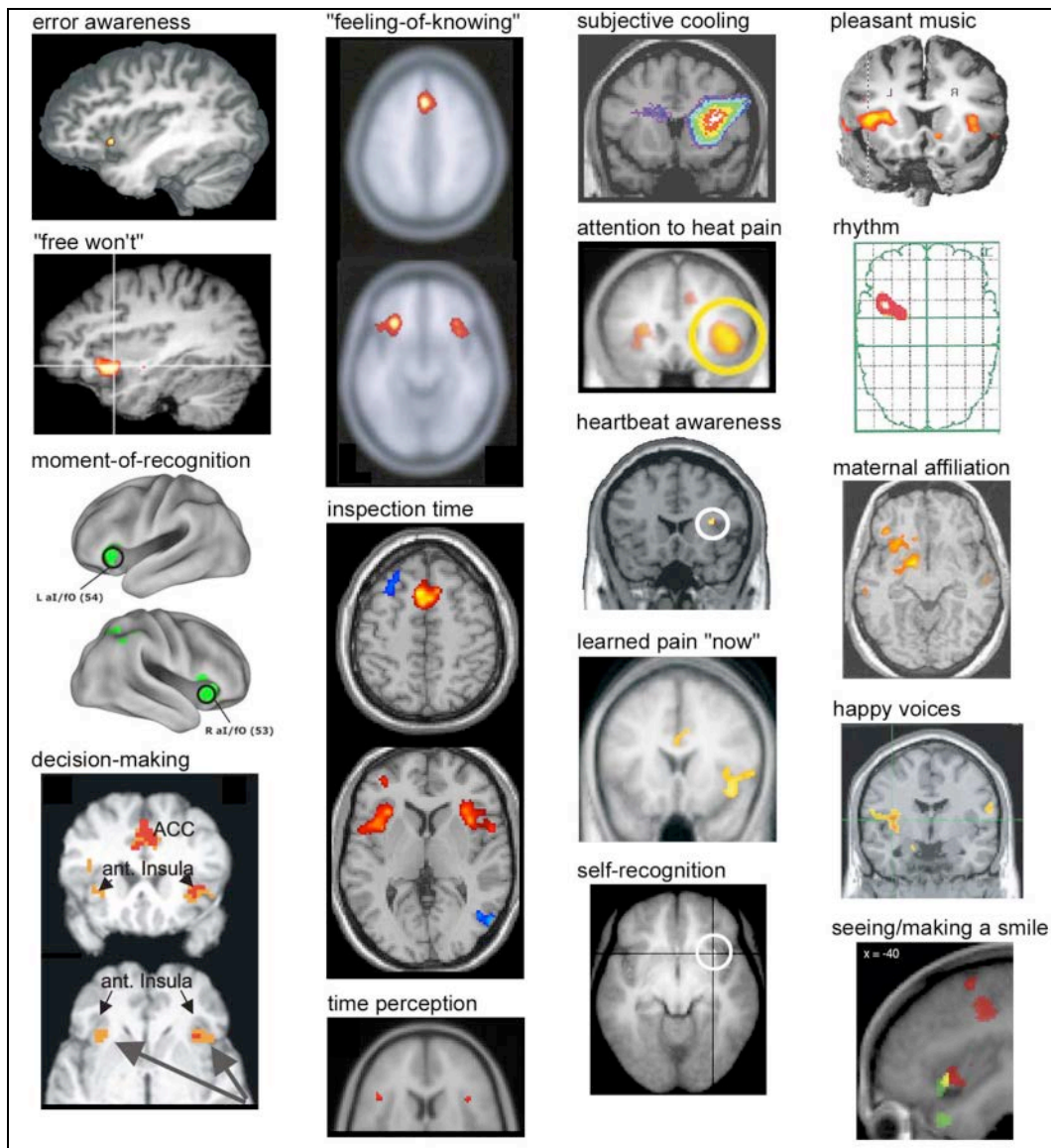
Figure 4: The anterior insula and human awareness (*Craig*, 2009).

Barrett, 2007; *Harrison* et al., 2010). From an evolutionary perspective, it makes sense that an integrated representation of the activity in all brain networks was needed in order to improve behaviour from the perspective of homeostatic efficiency. The goal of homeostatic efficiency (with respect to both the individual and the species) provides a plausible explanation of the progressive posterior-to-anterior integration in the insula.

A corollary VMpo projection to area 3a in sensorimotor cortex may relate cutaneous pain to (exteroceptive) somatic motor activity and to cortical control of spinal viscero-somatic reflex activity. In addition, a direct lamina I

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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). 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, and lamina I activity is relayed instead to ventrolateral orbitofrontal cortex through the submedial nucleus. Physiological and behavioural studies validate the primordial role of the ACC in homeostatic behaviour in rats (*Johansen* et al., 2001) and in the affective/motivational component of human pain by way of the direct lamina I path to MDvc.

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. In humans, an emotion can be defined as a feeling and a motivation; this directly supports the view of these feelings from the body as homeostatic emotions that reflect the survival needs of the body. Pain, temperature, and itch are homeostatic emotions that drive behaviour, just as hunger and thirst do (Craig 2002, 2003a, 2009). Convergent functional imaging data indicates that the anterior insula is associated with subjective feelings from the body and with virtually all human emotions, and so it seems to provide an image of the physical self as a feeling (sentient) entity (Figure 4). The association of the anterior insula with the subjective perception of pain, the anticipation of pain, the subjective reduction of pain (placebo analgesia), and the subjective generation of pain (hypnotic psychogenic pain) underscores the importance of the meta-representation of interoceptive state in the anterior insula for clinical understanding of the effects of emotion and belief on health. Furthermore, the recognition that sensual touch is included in the interoceptive system emphasizes the need to incorporate the neurobiological basis of conspecific human contact in therapies for emotional and physical health (*Björnsdotter* et al., 2009).

PAIN AS AN ASPECT OF HOMEOSTASIS

Pain is a homeostatic feeling. It has characteristics exactly comparable to other physical sensations (feelings) from the body. Pain normally originates with a change in the condition of the tissues of the body, a physiological imbalance that automatic (subconscious) homeostatic systems alone cannot rectify. It comprises a sensation, an affective behavioural drive and autonomic adjustments. Pain generates characteristic reflexive motor patterns, as do itch, hunger and rectal distension. The behavioural motivation of pain is normally correlated with the intensity of the sensory input, but this can vary under different behavioural, autonomic and emotional conditions, so that pain can become intolerable or it can disappear, similar to any other homeostatic emotions (e.g., hunger). However, unremitting pain that outlasts its homeostatic role is pathological.

Viewing pain as a homeostatic emotion provides a ready explanation of the interactions of pain with other homeostatic conditions (including temperature, blood glucose, blood pressure, level of arousal), because homeostasis is an integrated, dynamic process, and it explains the modulation of pain by homeostatic mechanisms. This conceptual perspective also provides a firm basis for explaining the interac-

tions of pain with emotional status or attention (i.e., the psychological dimension of pain), and it unifies the different conditions that can cause different types of pain from different tissues under a common homeostatic function - the maintenance of the integrity of the body. *Darwin* (1872) recognized that all animals respond with emotional behaviour to stimuli that in humans cause a feeling of pain. The new data reveal that noxious stimuli are represented in an evolutionarily ancient neural pathway that has the primary purpose of driving homeostatic mechanisms at spinal and brainstem levels and generating integrated behavioural motivation at the forebrain level. In primates, novel thalamo-cortical projections have emerged from this basic homeostatic system that provide encephalized cortical mechanisms for highly resolved sensations and motivations. Notably, sub-primates have the sub-cortical mechanisms that drive integrated homeostatic (emotional) behaviour, but they do not have these direct telencephalic pathways, and so they do not have the neuroanatomical capacity to feel pain in the same way that humans do.

The concept that human pain sensation is underpinned by a distinct and separate pathway for nociceptive-specific lamina I neurons to the primary interoceptive cortex in the dorsal posterior insula contradicts the conventional view that spinal lamina V ("wide dynamic range") neurons are "necessary and sufficient" for pain (*Price* et al., 2003). Evidence to the contrary has accumulated for years (*Craig*, 2003b), and recently the conventional view was definitively refuted by evidence that almost all such lamina V neurons convey Group II muscle afferent activity, respond tonically to limb position, and project directly onto ventral horn motorneurons and other motor-related sites. That is, such lamina V neurons are an integral component of the skeletal motor system (*Craig*, 2008). Recent functional imaging results on so-called "windup" (temporal summation of "second pain"; *Staud* et al., 2008) in fact corroborates strongly the fundamental role of lamina I spino-thalamo-cortical projections in pain. Nevertheless, in light of the fundamental role of the lamina I pathway in homeostasis, it would be more appropriate to call it a homeostatic afferent pathway than simply a "pain pathway" (*Craig*, 2006).

CONCLUSION

It is important to recognize that, contrary to the conventional textbook view, feelings from the body, such as pain or temperature, are neurologically distinct from tactile mechanoreception and proprioception at all levels. Such feelings from the body represent homeostatic afferent activity, that is, the sensory input representing the physiological condition of the body, which drives the central network that controls the ANS. The spinal and brainstem levels of the hierarchical homeostatic network are present in all mammals, but in humans there is a high-resolution representation of the condition of the body in primary interoceptive cortex in the posterior insula, which generates an energy-efficient map of all brain activity in the anterior insula that underpins the subjective "material me." Thus, there is a fundamental relationship between the physiological condition of the body and subjective feelings of all kinds.

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