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Interoception and Emotion: a Neuroanatomical Perspective

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Introduction

When someone asks, “How do you feel?”, your answer includes your bodily feelings as well as your emotional feelings. Influential models of emotion view the embodiment of emotions as fundamental; that is, many observers believe that interoceptive awareness has a crucial role in emotional awareness (Barrett et al., 2004; Damasio, 1993; James, 1890; Philippot et al 2002; Wiens, 2005). The neuroanatomical findings described in this chapter address the organization of pathways in the brain that engender feelings from the body, and they support the view that the neural substrates responsible for subjective awareness of your emotional state are based on the neural representation of your physiological state. These data show that there is a phylogenetically novel homeostatic sensory afferent pathway in primates, especially in humanoid primates, that provides the basis for a sense of the physiological condition of the body (“the material me”) in posterior insular cortex (Craig, 2002). A posterior-to-anterior progression of increasingly complex re-representations in the human insula provides a foundation for the sequential integration of your homeostatic condition with your sensory environment, with your motivational condition and with your social condition. Based on considerable evidence, I propose that this integration generates a unified penultimate meta-representation of the global emotional moment at the junction of the anterior insula and the frontal operculum (Craig, 2004a, 2005). Convergent functional imaging findings reveal that the anterior insula and the anterior cingulate cortices are conjointly activated during all human emotions (e.g., Murphy et al., 2003), which in my view indicates that the limbic sensory representation of subjective “feelings” (in the anterior insula) and the limbic motor representation of volitional agency (in the anterior cingulate) together form the fundamental neuroanatomical basis for all human emotions (Craig, 2002), consistent with the definition of an emotion in humans as both a feeling and a motivation with concomitant autonomic sequelae (Rolls, 1999). In this view, emotions are not simply occasional events, but rather are ongoing and continuous, and in this view emotional behaviors can occur without subjective feelings (as they do constantly in animals other than humanoid primates, or in unconscious human emotional acts). Thus, I concur with the idea that emotional behaviors evolved as energy-efficient means of producing goal-directed actions that fulfill homeostatic and social needs (Darwin, 1872), and I believe that our capacity for awareness of our emotional behaviors (that is, our subjective feelings) evolved because it enabled an enormous enhancement in the efficiency and complexity of emotional communication. I propose in this chapter that a neuroanatomical substrate for subjective emotional awareness exists in fronto-insular cortex as a finite set of repeated penultimate meta-representations of global emotional moments that extends across time, forming the basis not only for the continuity of subjective emotional awareness within a finite present but also for the uniquely human faculty of music – in fact, there are numerous convergent observations that lead to this proposal. Finally, these considerations also provide a homeostatic model that can explain the asymmetrical roles of the left and right forebrain in human emotion (Craig, 2005). These ideas may seem heuristic, philosophical, and speculative, but they arise directly from experimental findings in cat, monkey and human, as I will explain. These insights afford an opportunity to reclassify functional psychiatric disorders on a neurobiological basis, and they identify interoceptive processing regions that can serve as treatment targets for emotional problems (e.g., Simmons et al., 2006).

As a functional neuroanatomist, I study the organization of the brain using anatomical methods (e.g., tract-tracing) and physiological methods (e.g., microelectrode recordings) in comparative animals. I also use psychophysical and functional imaging methods (e.g., fMRI) in humans to test the predictions from comparative animal studies and to extrapolate these findings

into more highly evolved regions of the human brain. My research is based on the knowledge that the brain is not a mystical structure, but rather is reproducibly and evolutionarily well-organized for the purpose of maintaining and advancing both the individual and the species. The brain is not color-coded, its internal connections are not readily visible, its physiological operations are ephemeral, and it is organized in series of processing areas and nested hierarchies that form networks, so it is difficult to analyze. Studies of the effects of lesions and stimulation first identified the sensory regions (for vision, audition, and touch) and the motor regions (for skeletal movements and visceral activation) of the human cerebral cortex. Modern functional imaging studies, which produce color-coded maps of brain activation based on relative measurements of local cerebral blood flow during specific tasks, have validated these insights and are now being used in experimental psychology to reveal brain regions that are active during different cognitive and emotional tasks. However, such studies are constrained by inherent limitations in temporal, spatial and statistical resolution, and most importantly, by the fact that the underlying neural organization is generally not revealed by a top-down phenomenological approach (sometimes referred to as blob-ology; see Sternberg, 2000). By contrast, the findings described in the following text begin with a bottom-up view of ascending pathways associated with the sensory representation of the physiological condition of the body.

The data indicate that these pathways represent the ongoing status of all tissues and organs of the body, including skin, muscle, and viscera. I use the term *interoception* specifically to denote this generalized homeostatic sensory capacity, re-defining it from its original narrow usage to refer only to visceral sensation (Sherrington, 1948). The sensory afferents that represent the condition of the body subserve *homeostasis*, which is the ongoing, hierarchically organized neurobiological process that maintains an optimal balance in the physiological condition of the body. Homeostasis in mammals comprises many integrated functions and includes autonomic, neuroendocrine and behavioral mechanisms. Thermoregulation is a good example of a homeostatic function. The salient purpose of thermoregulation, as of homeostasis, is optimal energy management in support of life. All animals thermoregulate. The primordial means of thermoregulation in vertebrates is motivated behavior, similar to hunger and thirst. In humans, such affective motivations are accompanied by distinct homeostatic (interoceptive) “feelings”, and these modalities include not only temperature, pain, itch, hunger and thirst, but all feelings from the body, such as muscle ache, visceral urgency, and so-called “air hunger”. Consistent with the view that an emotion in humans consists of a sensation and a motivation with direct autonomic sequelae (Rolls, 1999), I regard these feelings as *homeostatic emotions* that drive behavior. In my opinion, they are virtually equivalent to the “background emotions” of Damasio (1994), and they are incorporated in the concept of core affect (Russell & Barrett, 1999; Barrett et al., 2004). The neuroanatomy of the forebrain pathways described below compel this concept.

Temperature sensation is an instructive example of a homeostatic emotion, because we normally think of it as an exteroceptive discriminative sensory capacity. However, the obligatory affect (pleasantness or unpleasantness) we feel with each temperature stimulus is the perceptual correlate of behavioral thermoregulatory motivation. This affect highlights the importance of temperature sensation for homeostasis, because it inverts depending on your body’s thermoregulatory needs (Cabanac, 1971; Mower, 1976). Thus, the cool glass of water that feels wonderful if you are overheated feels gnawingly unpleasant if you are chilled. Conversely, if you are chilled, then a hot shower feels wonderful, even if it is stinging and prickly, but it would be called painful if you were too warm. Similarly, if you remain in a room that is too chilly (or too warm) for energy-efficient thermoneutrality (or if you place your hand

on an object that is too cold or too hot), then you feel a growing discomfort (which when extreme is called painful) until you respond behaviorally in an appropriate manner. In the same way, eating salt or sugar is pleasant (and thus motivated) if the body needs it, but after you've eaten enough it becomes unpleasant and distasteful. These affective feelings reflect behavioral motivations that are driven by the homeostatic needs of the body, and the human perception of this combination of a feeling and a motivation is a homeostatic emotion. Note that homeostatically motivated behaviors occur in all animals and require no awareness of accompanying feelings. In fact, the structural absence in sub-primates of the forebrain homeostatic afferent pathways described below (specifically, the modality-selective interoceptive representation in the limbic sensory insular cortex and the direct motivational pathway to the limbic behavioral motor cortex in the cingulate region) implies that they cannot experience feelings from the body in the same way that humans do.

In the following text, I describe first the functional neuroanatomical evidence for an interoceptive (homeostatic afferent) pathway in primates, beginning with the development of spinal homeostatic afferent processing and the identified spinal neurons that represent each of the specific feelings from the body. I will detail the projections of these neurons to spinal, brainstem, and thalamo-cortical levels in monkeys, and then I will describe functional imaging studies in humans that validate these comparative findings. I will emphasize a particular functional imaging experiment which demonstrates graded activation of the dorsal posterior insula by cooling stimuli, because this finding validates the identification of the ascending interoceptive pathway and because it provides compelling neuroanatomical evidence for the concept of homeostatic emotions. In addition, the data in this particular experiment reveal the neuroanatomical progression of activity to the anterior insula that underlies subjective awareness of feelings of temperature. Next, I will summarize the convergent evidence for the role of anterior insula in all subjective emotional feelings, which substantiates the interoceptive basis for emotional awareness, and then I will describe how repeated meta-representations of global emotional moments can explain the observed role of this cortical region in awareness, time, and music. Finally, I will summarize a neuroanatomical model for left / right emotional asymmetry based on the homeostatic afferent processing pathways.

The functional anatomy of the ascending interoceptive pathway in primates

Specialized peripheral and central neural substrates that represent all homeostatic afferent activity generate the distinct feelings of pain, temperature, itch, muscle ache, sensual touch, and other bodily sensations by way of discrete sensory channels. This modality-selective sensory activity is conveyed first of all to hierarchically organized homeostatic integration and pre-autonomic response regions in the spinal cord and brainstem. An encephalized forebrain system that evolved virtually uniquely in primates surmounts the homeostatic response system and provides a direct cortical sensory image of the physiological condition of the body in the limbic sensory insular cortex and, in parallel, activates the limbic behavioral motor cortex in the medial frontal region (Fig. 1; for complete descriptions, see Craig 2002, 2003).

Small-diameter afferents. Small-diameter (A-delta and C) primary afferent fibers (which include nociceptors, thermoreceptors, osmoreceptors and metaboreceptors) report the physiological status of the various tissues of the body. These fibers terminate monosynaptically on projection neurons in the most superficial layer of the spinal (and trigeminal) dorsal horn (which is called lamina I or the marginal zone). The way the spinal cord develops reveals the special role of these fibers in homeostasis. During development, these small-diameter afferents

originate from a second wave of small neurons that emerge within the dorsal root ganglia subsequent to the large cells that generate the large-diameter fibers innervating mechanoreceptors and proprioceptors. The large-diameter fibers enter the spinal cord first and contact large dorsal horn neurons, and then the small-diameter fibers enter at the same time as the lamina I neurons appear. The lamina I neurons originate not from cells of the dorsal placode, but from progenitors of interneurons in the lateral horn (the sympathetic cell column), and they migrate to the top of the dorsal horn during a ventromedial rotation of the entire dorsal horn at precisely the right time during development to meet the incoming small diameter afferents. This delicately coordinated ontogenetic sequence indicates that together the small-diameter afferents and the lamina I neurons constitute a cohesive system for homeostatic afferent activity that parallels the efferent sympathetic nervous system. In contrast, the large neurons that receive large-diameter fiber input come to lie at the base of the dorsal horn (because of the rotation) and serve as interneurons for skeletal motoneurons. The small-diameter afferent fibers in cranial parasympathetic nerves (e.g., vagus and glossopharyngeal) that innervate visceral organs terminate similarly in the nucleus of the solitary tract in the caudal medulla. These pathways represent, respectively, the afferent inputs for the sympathetic and the parasympathetic halves of the autonomic nervous system

Lamina I neurons. Consistent with this developmental view, the projections of lamina I neurons convey small-diameter homeostatic sensory afferent input directly to the homeostatic integration and control regions in the spinal cord and brainstem. Lamina I projections thus provide the substrate for the hierarchical, modality-selective somato-autonomic reflexes activated by spinal small-diameter afferents that are crucial for homeostatic function (Sato & Schmidt, 1970).

In the spinal cord, their major projection is to the autonomic cell column of the thoracolumbar spinal cord, where sympathetic pre-ganglionic output neurons are located. In the brainstem, lamina I neurons project exclusively to recognized homeostatic integration sites, including the ventrolateral medulla, the catecholamine cell groups A1-2 and A5-7, the parabrachial nucleus (PB), and the periaqueductal gray (PAG). They converge at these sites with afferent activity associated with the parasympathetic system by way of the solitary nucleus. These sites are all heavily interconnected with the hypothalamus and amygdala. The crucial role of lamina I in homeostatic reflexes is highlighted by the fact that lamina I and the spinal autonomic cell columns are the only spinal sites that receive descending modulation directly from brainstem and hypothalamic pre-autonomic sources.

Lamina I neurons comprise several modality-selective classes that can be regarded as virtual “labeled lines” for distinct feelings from the body, such as first (sharp) pain, second (burning) pain, cool, warm, itch, sensual touch, muscle ache and cramp, etc. (although their activity must be integrated in the forebrain; see Craig, 2003). Each class consists of a morphologically distinct type of neuron that receives input from a specific subset of small-diameter afferents. Quantitative analyses using extracellular recordings from single lamina I neurons indicate that the response characteristics of these cells correspond very well with the psychophysical characteristics of these distinct sensations (Craig et al., 2001; Craig, 2004b). For example, the cooling-sensitive thermoreceptive-specific neurons that are uniquely found in lamina I respond linearly to innocuous cooling (Fig. 2A) and saturate at noxious cold temperatures, like human cooling sensitivity. Intracellular recording and staining showed that such cells are uniformly pyramidal-shaped lamina I cells (Fig. 2B). In contrast, the polymodal nociceptive lamina I cells are selectively sensitive to noxious heat, noxious pinch, noxious cold

and are monosynaptically activated by C-fibers, and their responses to repeated brief-contact heat and the thermal grill (an illusion of pain) correspond in all respects with the psychophysical characteristics of the human sensation of second (“burning”) pain. Such cells are multipolar lamina I neurons (Fig. 2B). The selectivity of lamina I spinothalamic tract (STT) neurons is convincingly demonstrated by the sub-population of cells that have characteristics which uniquely correspond with the human sensation of itch (Andrew & Craig, 2001).

Whereas lamina I is usually thought of as a “pain and temperature” site, its role in homeostasis is clearly revealed by the neurons that respond selectively to small-diameter afferent input from muscle. Such afferents subserve ongoing homeostatic adjustments to muscular work, but when strongly activated they are also directly responsible for the feelings of muscle burn, pain, and cramping. The co-mingling of these muscle-selective neurons in lamina I with other cells selectively responsive to temperature or pain or itch emphasizes the fundamental perspective that lamina I neurons convey afferent activity representing all aspects of the physiological condition of all tissues of the body. It is also important to recognize that lamina I neurons do not simply provide emergency signals, but rather are engaged in homeostasis *on an ongoing basis*, just as cardiorespiratory activity is continuously affected by ongoing muscular activity and by ongoing temperature changes. Furthermore, many small-diameter afferents are sensitive to cytokines, opioids, steroids, hormones (e.g., somatostatin), and other local and circulating immune modulators, consistent with the role of sympathetic and parasympathetic autonomic efferents in the regulation of immune and neuroendocrine functions.

Lamina I projections to the primate forebrain. High-resolution tract-tracing experiments revealed that, in primates, lamina I neurons project to the contralateral thalamus in the lateral spinothalamic tract, which ascends at the precise location within the spinal cord where cordotomy lesions in humans interrupt feelings from the body such as pain, temperature, itch, sensual touch, and so on (Fig. 1; Craig, 2002, 2003). In sub-primates, ascending lamina I activity is processed mainly in brainstem sites (e.g., A1, PB and PAG), which then provide a highly integrated signal to emotional behavioral control regions in the forebrain. Encephalization in primates produced a somatotopographic, modality-selective lamina I spinothalamic projection to a specific thalamo-cortical relay nucleus (VMpo) that in turn projects to a discrete portion of dorsal posterior insular cortex (dpIns, or interoceptive cortex). A parallel pathway, also unique to primates, conveys afferent input from the vagal and glossopharyngeal nerves by way of the nucleus of the solitary tract to a rostrally adjacent thalamo-cortical relay nucleus (VMb), which in turn projects to a rostrally adjacent region of dorsal insular cortex. (The “insula” is a cortical “island” buried within the lateral sulcus that has intimate connections with amygdala, hypothalamus, and cingulate and orbitofrontal cortices) Together these pathways through VMpo and VMb provide a direct cortical image of all homeostatic afferent activity that mirrors the sympathetic and the parasympathetic halves of the efferent autonomic nervous system. The VMpo in the human thalamus is greatly enlarged relative to the macaque monkey.

The ascending projections of lamina I neurons in primates also provide a direct thalamo-cortical pathway that activates the anterior cingulate cortex (ACC) by way of a medial thalamic relay (MDvc). By contrast, in sub-primates the medial thalamic sources of input to the ACC receive integrated homeostatic input from the brainstem (PB and PAG). (In cats and rats, there is instead a direct lamina I projection to a neighboring, developmentally related nucleus in medial thalamus (nucleus submedius), which projects to ventrolateral orbitofrontal cortex, associated with hedonic integration and descending anti-nociception, rather than to the ACC.) I concur with the suggestion made previously by several neuroanatomists (e.g., W. Nauta, M. Mesulam, G. Van

Hoesen) that the insula can be regarded as limbic sensory cortex, because of its association with homeostatic afferent activity and the amygdala, hypothalamus, and orbitofrontal cortex, and that the anterior cingulate cortex can be regarded as limbic motor cortex, because of its association with homeostatic efferent (autonomic) activity and its descending projections to the PAG in the brainstem. This fits well with the modern view of the overall organization of frontal cortex into limbic sensory and limbic motor networks (Ongur & Price, 2000).

Functional imaging of interoception in humans

Activation of dorsal posterior insula. Functional imaging, lesion and stimulation studies in humans confirm the crucial role of the dorsal insula in graded pain, graded temperature, graded itch, dynamic or painful muscle sensation, sensual touch, hunger, thirst, gustation, cardiorespiratory activity, “air hunger”, etc. (for refs., see Craig, 2002, 2003) . It serves as primary sensory cortex for each of these distinct interoceptive “feelings” from the body. Accumulating evidence indicates: that it is activated in a graded manner during each of these sensations; that stimulation of this region (or VMpo / VMb) can produce these sensations; and that lesions which include dpIns (or VMpo / VMb) can selectively disrupt these sensations. Notably, dpIns is delimited by labeling for the receptors of corticotropin releasing factors, which many investigators regard as a definitive marker for homeostasis (Sanchez et al., 1999). The primordial role of the insular cortex is modulation of brainstem homeostatic integration, which are the main targets of its descending projections. Thus, the interoceptive cortical image of the physiological condition of the body in humans emerged evolutionarily as an extension of the hierarchical homeostatic system. In other words, feelings from the body in humans reflect its homeostatic condition.

The experimental tract-tracing findings in monkey indicate that the lamina I input to VMpo, and also the cortical projections of VMpo and VMb to dpIns, are topographically organized in the anterior-to-posterior direction (face to foot). The neuroanatomical findings in the monkey predict that all homeostatic afferent modalities will produce graded activation in dpIns that is arranged somatotopographically in the antero-posterior direction. Recent fMRI evidence has demonstrated this somatotopic gradient for sensations of heat pain and innocuous cooling in the dpIns of humans (Brooks et al., 2005; Hua et al., 2005). Significantly, this gradient is orthogonal to the lateral-to-medial (face to foot) organization of the main somatosensory thalamus and the S1 and S2 somatosensory cortices. This contrast substantiates the differentiation of dpIns; in particular, it highlights the distinction of dpIns from S2, to which pain-related activation in the operculo-insular region has often been incorrectly ascribed. This also means that the large-diameter afferent lemniscal pathway to the somatosensory thalamus (VPM / VPL) and the small-diameter afferent pathway to VMpo / VMb develop along different neurotrophic gradients, which substantiates the concept that the VMb and VMpo representation of homeostatic afferents (which control smooth muscle) is separate from the main somatosensory representation of mechanical and proprioceptive inputs (which control skeletal muscle). That is, there are two fundamentally different thalamo-cortical representations of somatic afferent activity in the human brain, and the primary interoceptive cortex in the posterior insula is a distinct entity.

Activation of anterior cingulate. Many functional imaging studies have documented the role of the human ACC in behavioral drive and volition (behavioral agency; which seems to be guided dynamically by error likelihood estimation, see Brown and Braver, 2005), and the ACC is activated by homeostatic afferent activity. The ACC is activated in nearly all functional imaging studies of pain, and it is similarly activated in studies of muscle and visceral sensation. Functional

imaging studies of the thermal grill illusion of pain (Craig et al 1996) and of hypnotically modulated pain unpleasantness (Rainville et al., 1997) associate ACC activity directly with the affective motivation of pain (unpleasantness) and indicate that this pathway engenders the affect and motivation that render pain a homeostatic emotional drive. The conjoint activation of dpIns and ACC by the distinct homeostatic modalities seems to correspond well with the idea that the feelings from the body constitute homeostatic emotions that simultaneously generate both a sensation and a motivation. That is, temperature, pain, itch and muscle ache are homeostatic emotions that drive behavior, just as hunger and thirst are, and the condition of our bodies directly affects our feelings and our motivations on an ongoing basis. The activation of the region of the ACC by innocuous thermal stimuli described in the next section is particularly instructive.

Functional imaging of temperature sensation: an example of a homeostatic emotion.

Activation of posterior insula and anterior cingulate. Temperature, like pain and itch, is a feeling from our bodies that we normally externalize. We readily detect the temperature of an object or of the environment. Temperature sensation has always been regarded as a discriminative exteroceptive cutaneous sensory capacity allied with the sense of touch. However, the thermoreceptors in our skin, muscles and viscera actually report local tissue temperature, and thermoregulation is necessary for all animals to use energy most efficiently. The functional anatomy of temperature sensation in humans reflects the primordial importance of temperature sensibility for homeostasis. The location of the discriminative thermosensory cortex identified by the PET imaging data in Figure 3 fits precisely with the location of dpIns identified by the functional anatomical tracing studies in the monkey (Craig et al., 2000; see also Maihofner et al., 2004; Hua et al., 2005). Figure 3 shows three different analyses of brain activation observed using PET imaging during the application of six different cool temperatures on the palm of the hand. The first row, a simple contrast between the highest and lowest temperatures, served as a mask for subsequent analyses. The second row shows a regression analysis against thermode temperature, which reveals that activation of one site in the contralateral cortex was directly correlated with objective temperature (the red blob on the left side at level 24). This site can therefore be regarded as primary thermosensory cortex. Its location in the dorsal posterior insula (dpIns) explains clinical reports of stroke-induced lesions that produced thermanesthesia (Schmahmann & Liefer., 1992; Greenspan et al., 1999). Strikingly, this region is not part of the somatosensory cortices that represent touch sensation, which lie on the parietal surface (postcentral gyrus) and in the parietal operculum. Rather, the role of insular cortex as limbic sensory cortex fits neatly with the view that temperature sensation is first and foremost of importance for homeostasis. In addition, more recent PET and fMRI evidence reveals that cooling a large region and dynamic cooling produce graded activation at a site in the medial frontal cortex (in the limbic behavioral motor cortex near the ACC) adjacent to the site that is activated during pain (Egan et al., 2005; Hua et al., 2005). Together these findings support the view that temperature produces both a “feeling” and a behavioral motivation in humans, that is, a homeostatic emotion.

Activation of anterior insula related to subjective feelings of temperature. So, how do we “feel” temperature? Our subjective sense of innocuous temperature is very linear, but it is not perfect. The deviation is sufficient to provide a robust statistical difference between cortical activation associated with subjective rather than objective temperature. The third row in Figure 3 shows a regression analysis of the same data set against the participants’ subjective ratings of coolness. A large area of activation in the anterior insula and orbitofrontal cortex on the right

side is conspicuous in these data. Close comparison of the activation blobs at level 24 in rows 2 and 3 reveals that in the subjective regression analysis a new activation site appears just anterior to the main site activated in dpIns in the objective temperature regression analysis. Thus, these data indicate that there is an immediate re-representation of thermosensory activation in the middle insula on the homolateral side, just anterior to dpIns. This re-representation must be an abstracted or integrated re-representation, in some sense, because its activity is significantly more closely related to subjective ratings than to objective temperatures. The data show a subsequent commissural transfer from the middle insula to a lateralized series of re-representations in the anterior insula and orbitofrontal cortex on the right side, which are much more strongly correlated with subjective feeling. This is a neurobiologically parsimonious pattern of activation, because progressive re-representations that combine feature extraction and cross-modality integration are present in the serial processing streams observed in the visual, auditory, and parietal somatosensory cortical regions and are consistent with the evolutionary development of new processing regions in primate cortex (Krubitzer & Kaas, 2005). The lateralization is crucial evidence of hemispheric specialization; I will return to this issue further below.

Functional imaging of subjective feelings in humans

Thus, the PET imaging data on temperature sensation illuminate an anatomical model in which the subjective awareness of feelings from the body is generated directly from cortical re-representations of the interoceptive image of the body's homeostatic condition. The results of many other imaging studies of subjective feelings in humans correspond with this anatomical model. These convergent data suggest that the cortical interoceptive image of the body provides the basis for awareness of the "material me", or the sentient self.

The data show an anatomical progression of activity from dpIns, first to the mid-insula on the homolateral side, and then, by way of a commissural lateralization, to the right anterior insula. The posterior to anterior progression of processing in the insular cortex is consistent with several neuroanatomical considerations, most particularly with the enormous phylogenetic expansion of anterior insula across humanoid primates (Allman et al 2005). (Notably, in monkeys, interoceptive cortex seems to project directly to orbitofrontal cortices and does not generate the successive re-representations in anterior insular cortex that seem to be unique to humanoid primates.) Other imaging findings support the convergence in the middle insula of activity associated with emotionally salient stimuli of all modalities, in part by way of interconnections with the amygdala. The chart in [Figure 4](#) summarizes my view of the anatomical organization of progressive integration in insular cortex, which is based on numerous anatomical and imaging reports (e.g., Chikama et al., 1997; Brooks et al., 2002; Adolphs, 2000; Ollausson et al., 2004). This chart illustrates the concept that progressive re-representations of the physiological (interoceptive) condition of the body provide the basis for the integration of homeostatic afferent activity, first in the middle insula with emotionally salient inputs from all sensory modalities and from sub-cortical homeostatic control regions (hypothalamus and amygdala), and then in the anterior insula with emotionally salient activity in other limbic cortical regions (ACC, orbitofrontal cortex) as well as with the cortical region involved in contextual planning (dorsolateral prefrontal cortex). Thus, this posterior-to-anterior progression of re-representations in the human insula provides a foundation for the sequential integration of the homeostatic condition of the body with the sensory environment, with internal autonomic state, with motivational conditions and finally with social conditions. This progression culminates in the most recently evolved regions of the anterior insula, situated at its junction with the frontal operculum and orbitofrontal cortex.

This anatomical view of homeostatic emotional integration is directly supported by evidence that activation of right anterior insula (rAI) is correlated not only with subjective ratings of temperature, but also with subjective attention to pain (of either cutaneous, muscular or visceral origin) (e.g., Brooks et al., 2002). The anatomical posterior-to-anterior progression can explain why activation associated with anticipation of pain and feelings of chronic pain localize in a more anterior portion of rAI than activation during acute experimental pain (Schweinhardt et al., 2006). Furthermore, activation in rAI is correlated with subjective ratings of disgust or trustworthiness, with internally generated emotions like anger, sadness, happiness, lust, and fear, with imitation or empathic referral of these emotions, with empathic feelings of pain imputed to a loved one, and even with feelings of social exclusion (for refs. see Craig, 2002). So, the convergence of these findings supports the view that the cortical re-representations in rAI of the interoceptive image of the body's physiological condition provides a basis for the subjective awareness of *all* emotional feelings. The culmination of this integration may involve different modules that together produce a unified penultimate meta-representation that I refer to as a *global emotional moment*. This convergent integration is supported by demonstrations of synergistic activation of anterior insula by interoceptive feelings and emotions (e.g., Phillips et al., 2003).

These neuroanatomical data substantiate the view that the cortical image of subjective feelings is built upon the homeostatic (interoceptive) hierarchy. The association of rAI with subjective awareness of all emotions fits well with the idea that human emotions are based in part on feelings from the body, which is the essence of the James-Lange theory of emotion (James, 1890). The meta-representations of the state of the body in rAI seem to differentiate inner from outer conditions (self from non-self) and provide a subjective mental image of the material self as a feeling (sentient) entity that is utilized during all emotional states — in other words, it seems to provide the anatomical basis for emotional awareness. As discussed in greater detail in Craig (2002), this fits with the anatomical features of the so-called “somatic marker” hypothesis of consciousness (Damasio, 1994). The latter concept predicts that interoceptive state and emotional feelings are directly related, which is supported by recent evidence of distinct patterns of homeostatic activity during different emotions (Deichert et al., 2005; Rainville et al., 2006). The interoceptive re-representations in rAI provide a substantive neural basis for these relationships and, as well, for the “as-if” loop that Damasio postulated would enable mental interoceptive predictions of the consequences of emotional behaviors based on prior experiences.

It is important to note explicitly that this integration in the anterior insula includes not only emotionally salient sensory inputs, but also the activity within the motivational regions of the brain itself (i.e., ACC and orbitofrontal cortices, ventral striatum). Notably, the integration of the behavioral agent with the “feeling self” can provide an anatomical basis for the representation in awareness of the illusory “I” postulated by Damasio. Interestingly, studies of placebo analgesia reveal coordinated activation of ACC and rAI, suggesting that the integration in rAI of the activity in the ACC (the behavioral agent) not only produces a representation of motivation within subjective emotional awareness, but also enables motivation to directly modulate subjective feelings. This interpretation offers an explanation for the paradoxical finding that activity in rAI *increases* with placebo analgesia rather than being reduced in some studies (Petrovic et al., 2002). This perspective also negates a main criticism of the James-Lange theory, i.e., that it did not allow for feelings of internally generated emotion, and by incorporating the likelihood that anterior insula stores representations of past interoceptive / emotional experiences, it enables ready explanations of the interactions between homeostatic functions and emotional states, for example in somatization and psychosomatic illness.

An anatomical model for subjective awareness of feelings, agency and time.

Thus, a refined and integrated image of the state of the body seems to provide the basis for awareness of the “feeling self”. In this homeostatic model, the representation of the global emotional moment includes feelings about motivations, and it can be modified by expectations and motivations, based on interconnections between anterior insula and ACC (as well as sub-cortical structures, such as amygdala and ventral striatum, and the dorsolateral prefrontal cortex). In this view, the co-activation of the anterior insula and the ACC during all emotions not only corresponds with the view that an emotion is both a feeling and a motivation, but also provides the active behavioral agent that is missing from the “somatic marker” hypothesis. This interpretation is anatomically consistent with the dual lamina I spinothalamocortical projections (to insula and cingulate) and with the overall anatomical organization of primate frontal cortex into medial (limbic behavioral motor) and insular / orbital (limbic sensory) networks (Ongur & Price, 2000).

Anterior insula and awareness. The role of rAI in interoceptive awareness and subjective feelings is supported by the demonstration by Critchley et al (2004) that activation of rAI is uniquely correlated with subjective perception of heartbeat timing, a classic test of interoceptive awareness (see discussion by Craig, 2004). This fits with psychological evidence associating interoceptive (heartbeat) awareness with self-reports of emotional experience (Barrett et al., 2004). Yet, the analyses by Critchley et al. (2004) were based on subjective perceptions of cross-modal timing, and in fact, graded, selective activation of rAI (and ACC) is produced during other cross-modal timing disparities, for instance in the ventriloquism illusion (Bushara et al., 2000). In addition, there is strong evidence of a direct relationship between activation in rAI and subjective awareness of timing, by using either long or short expected intervals, or by using injections of clonidine to produce subjective temporal slowing, or by using graded attention to timing in a multi-cue task (summarized in Coull, 2004). Nevertheless, selective activation of anterior insula and anterior cingulate bilaterally was strongly *inversely* correlated with display time (and performance) in a backward masking task that probed the temporal limits of visual observation during brief sub-second presentations (Deary et al., 2004). In my opinion, this very striking result, considered together with these other findings, indicates that the fundamental role of anterior insula may be described most simply as subjective awareness. This inference can explain reduced activation of these same regions during momentary lapses in attention and increased activation during the effort that follows such lapses (Weissman et al., 2006). After highlighting a unique type of neuron in rAI, I will outline a structural proposal for this inference.

Von Economo neurons. Allman et al. (2005) recently reported that a population of large spindle neurons, which they call Von Economo neurons (after an early neuroanatomist), is uniquely found in the anterior insula (or fronto-insular region) and anterior cingulate of humanoid primates. Most notably, they reported a trenchant phylogenetic correlation, in that spindle cells are most numerous in aged humans, but progressively less numerous in children, gorillas, bonobos and chimpanzees, and nonexistent in macaque monkeys, a progression which parallels the results of the mirror test for self-awareness (Macphail, 1998). They hypothesize that the fronto-insular cortex may subservise “intuition”, because it is activated in studies of uncertainty and anxiety, and they propose that the Von Economo spindle neurons provide the basis for large-scale integration and fast communication between the two sides of cortex. It seems likely to me that the Von Economo spindle neurons interconnect the most advanced portions of limbic sensory (AI) and limbic motor (ACC) cortices, both ipsilaterally and contralaterally, which, in sharp contrast to the tightly interconnected and contiguous sensorimotor cortices, are situated physically far apart as a consequence of the pattern of evolutionary development of limbic cortices. Thus, analogous to the need for fast

interconnections between somatosensory and motor cortices for playing the piano, the spindle neurons could enable fast, complex and highly integrated emotional behaviors.

A structural model for awareness and music in the anterior insula. Thus, an alternative hypothesis to the concept of “intuition” is the idea that the Von Economo spindle neurons, by interconnecting advanced limbic sensory and motor cortices, provide the anatomical basis for the generation of unified penultimate meta-representations of global emotional moments, and indeed, for a series of such meta-representations across time. This hypothesis is based not only on the foregoing functional anatomical considerations, but also on growing evidence that AI is associated with music. Functional imaging studies indicate that listening to music or covertly imagining music strongly activates anterior insula (Ackermann & Riecker, 2002), and clinical studies indicate that restricted lesions of anterior insula can produce a condition known as amusia, or disruption of the ability to appreciate the emotional content of music. Music is a uniquely human faculty that has the profound capacity to bind us together emotionally and to change both our emotions and our subjective perception of time. Music can be described as the rhythmic temporal progression of emotionally laden moments — which suggests a very straightforward structural model for awareness, because a rhythmic progression of global emotional moments can easily be represented by a sequence of quantal anatomical units (Craig, 2004). (It is interesting to note here my observation that bonobos, who seem to me to be remarkably aware and who uniformly pass the mirror test, clearly use rhythm to communicate - synchronous rhythms for agreement and contrapuntal rhythms for disagreement and negotiation - whereas common chimpanzees do not; see also Macphail 1997; De Waal, 2002; Williams, 1998)

That is, if the progressive homeostatic emotional integration in the anterior insula does attain the concise representation of a global emotional moment (i.e., including all emotionally salient aspects of the homeostatic, sensory, autonomic, motivational and social conditions, as described above), then development of the ability to represent each emotional moment *across time* would obviously be an enormous evolutionary advantage. A quantal series of such meta-representations of feelings across time (from the past into the future) would directly enable the perception of autobiographical emotional continuity, the backward recognition of emotionally salient behavioral patterns, and the forward anticipation of emotional consequences (i.e., Damasio’s “as-if” loop). Such an anatomical structure could engender awareness, because it would provide a cortical image of the self as a continuous sequence of sentient emotional moments (that could not “see” itself, just like “consciousness”). This anatomical structure could also directly underlie the rhythmic emotional progression of music. And, of course, repetition of the structural unit representing a global emotional moment to produce a sequence of such moments would be a natural and easily realizable neuroanatomical development evolutionarily. Evidence for the association of anterior insula with emotional value estimation in a temporal difference model of interoceptive learning (Seymour et al., 2004) and with interoceptive prediction in anxiety (Paulus and Stein, 2006) provides support for this model.

Because the number of quantal representations of global emotional moments must be anatomically constrained and finite, its magnitude would correlate with the duration of the subjective emotional present. Thus, one prediction of this model would be that moments of heightened awareness would be characterized by an altered perception of time. Intriguingly, the phrase “time stood still” is often used to describe moments of heightened awareness. A finite absolute number of quantal global moments would mean that, during such moments of heightened awareness, the absolute extent of the subjective perceptual present must be shortened — as finite resources were allocated to maximize representation of the present in real time, each

global emotional moment would represent a shorter temporal duration, and the total extent of time represented across the total pool would be shorter. This seems intuitively obvious, and there may be quantitative psychometric data addressing this prediction that I have not found, but the only evidence of which I am aware associating the temporal focusing of awareness with neural activation is the aforementioned study by Deary et al. (2004).

Another prediction would be that the loss of such an anatomical structure would be associated not only with amusia, but also with a condition in which the self would not have emotional salience across time. In fact, whereas lesions of posterior insula can produce discrete loss of pain and temperature sensations, lesions of anterior insula can reportedly produce conditions regarded clinically as “anosognosia” (the lack of emotional awareness of one’s self; Karnath et al., 2005) or “anergia” (complete listlessness; Manes et al., 1999). Congenital disruption of the insula bilaterally is found in children with Smith-Magenis syndrome, which is characterized by mental retardation and lack of emotional coordination (Boddaert et al., 2004). Of course, although I have focused my comments on the “feeling” side of the limbic cortical system, it is crucial to remember that, if the von Economo neurons interconnect anterior insula and anterior cingulate, consistent with the conjoint activation of both sites during all emotions and during the experiment of Deary et al (2004), then lesions of the anterior cingulate could produce closely related motivational dysfunctions. For example, the ACC has been associated with alexithymia in several studies (e.g., Kano et al., 2003). Further work in this direction is certainly needed.

Homeostatic and emotional asymmetry in the forebrain

The homeostatic model of human emotional awareness presented in the preceding text is lateralized to the anterior insula and anterior cingulate on the right side. That fits with an established psychophysiological model, in which emotion is more strongly associated with the right forebrain. However, psychophysiological evidence has accumulated indicating that the left and right halves of the human forebrain differentially associate with particular emotions and affective traits. That is, reviewers of literature relating affect and emotion to EEG activity, cortisol secretion, immune function, and functional imaging of brain activity have concluded that positive/negative valence, approach/withdrawal behavior, and/or affiliative/personal relevance are associated with left/right hemispheric forebrain activity, respectively, albeit with possible underlying circuits predominantly used for particular emotions (Heilman, 2000; Davidson, 2004; Allen and Kline, 2004; Wager et al., 2003; Murphy et al., 2003). I recently proposed that forebrain emotional asymmetry in humans is anatomically based on an asymmetrical representation of homeostatic activity that originates from asymmetries in the peripheral autonomic nervous system (Craig, 2005).

Briefly, this proposal suggests that emotions are organized according to the fundamental principle of autonomic opponency for the management of physical and mental energy. In this homeostatic neuroanatomical model of emotional asymmetry, the left forebrain is associated predominantly with parasympathetic activity, and thus with nourishment, safety, positive affect, approach (appetitive) behavior, and group-oriented (affiliative) emotions, while the right forebrain is associated predominantly with sympathetic activity, and thus with arousal, danger, negative affect, withdrawal (aversive) behavior, and individual-oriented (survival) emotions. In this model, management of physical and mental (meaning neural) energy is the salient organizational motif (as for homeostasis), such that energy enrichment is associated with the left forebrain and energy expenditure is associated with the right forebrain, consistent with the

respective roles of the parasympathetic and sympathetic efferent systems. In this model, the evolution of matching homeostatic afferent and autonomic efferent asymmetries in the humanoid forebrain provided another substantial improvement in the efficiency of emotional control and communication, thereby facilitating increasingly complex social interaction (leading ultimately to deictic signalling, language, and civilization). For example, it implies that the homeostatically parsimonious role of the left insula in (parasympathetic) emotional affiliation may be the basis for the crucial association of left anterior insula (which is now included in Broca's area) in verbal emotional communication and the predominant use of the contralateral (right) hand in deictic pointing among humanoid primates (De Waal, 2002). This model explains the predominant activation of right anterior insula in studies of elicited emotion by sympathetic arousal and it is compelled by the strong activation of left anterior insula in studies of maternal or romantic love and during compassionate or empathic feelings (for refs., see Craig, 2005).

Coordinated opponent interactions between the two hemispheres, mirroring the autonomic principle of coordinated opponency, can provide a fundamental management process. The analogy of driving a car is useful – rather than placing your hands at opposite sides of the steering wheel, it is more efficient if you place your hands at the two o'clock and ten o'clock positions, because then you can drive by exerting a steady downward pressure with one hand and simply varying the downward pressure with the other hand. This is exactly how the coordinated autonomic control of the heart functions; tonic sympathetic drive is modulated by rapid variations in parasympathetic drive. I propose that the forebrain coordinates emotional control in the same manner. Notably, the salient purpose of homeostasis is optimal energy management, and the efficient use of energy in the brain, which overall consumes about 25% of the body's entire energy budget, must be a potent evolutionary pressure. This model instantiates neurobiologically the psychological proposal that a hypothetical "calm and connection system" opposes the arousal/stress system (Uvnas-Moberg et al., 2005). It can incorporate the bivalent concept of emotion, in which positive and negative affects are different psychological dimensions, and also the core affect concept, in which energization is a key dimension (Barrett et al., 2004; Zautra, 2003; Phillipot et al., 2002).

Thus, the model provides a structural basis for suggesting that coordinated opponent interactions between left and right insula and cingulate are fundamentally important. Positive and negative affect interact in an opponent fashion; for example, it is well documented that social engagement (and oxytocin) can suppress arousal, stress, depression, and cortisol release, whereas conversely, the latter factors can reduce mood, sociability, and immune function (Heinrichs et al., 2003; Zautra, 2003). This model proposes that the relative balance of activity within symmetrical modules in the left and right insula and cingulate may be of critical significance for neurophysiologically coordinated emotional complexity, or mental health.

For further elucidation of this proposal, see Craig (2005). Recent findings add to the evidence cited in that article by showing (1) that asthmatic (vagal bronchiopulmonary) afferent activity is associated with left insular activation (Rosenkrantz et al., 2004), (2) that emotionally pleasing music, if chosen individually by the subjects, activates the left anterior insula more strongly than the right (Koelsch et al., 2006), (3) that a patient with a selective lesion of the left anterior insula experienced a selective loss of musical enjoyment (Griffiths et al., 2005), and (4) that covert singing at different tempos produces a strikingly clear asymmetry in anterior insular activation consistent with the temporal effects of sympathetic and parasympathetic activity on heart rate (Ackermann & Riecker, 2004).

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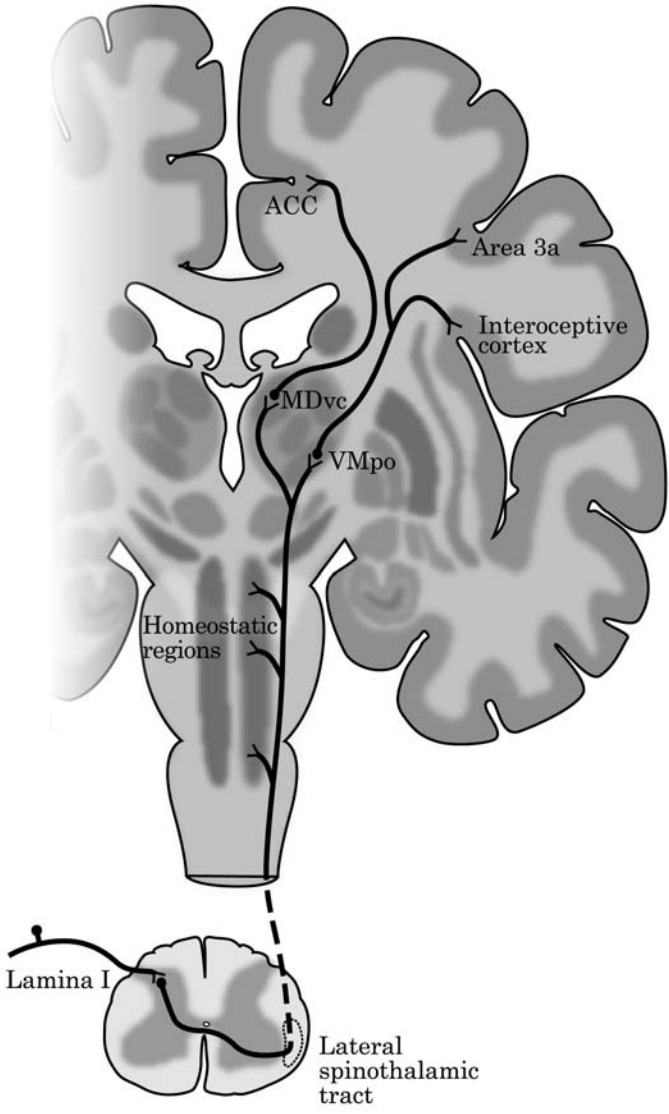
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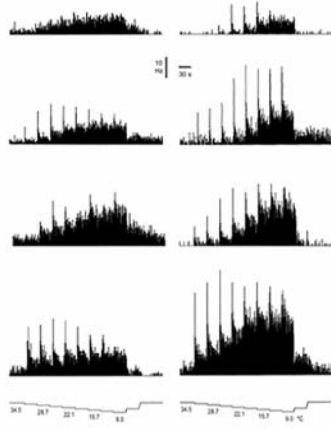
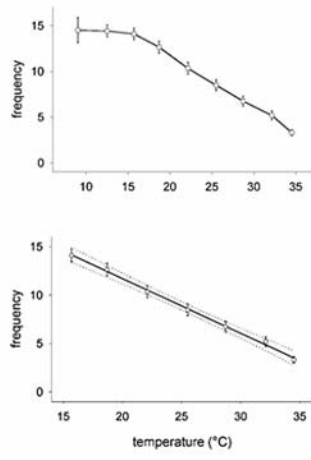
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