OPINION

The nature of feelings: evolutionary and neurobiological origins

Antonio Damasio and Gil B. Carvalho

Abstract | Feelings are mental experiences of body states. They signify physiological need (for example, hunger), tissue injury (for example, pain), optimal function (for example, well-being), threats to the organism (for example, fear or anger) or specific social interactions (for example, compassion, gratitude or love). Feelings constitute a crucial component of the mechanisms of life regulation, from simple to complex. Their neural substrates can be found at all levels of the nervous system, from individual neurons to subcortical nuclei and cortical regions.

Survival depends on the maintenance of the body's physiology within an optimal homeostatic range. This process relies on fast detection of potentially deleterious changes in body state and on appropriate corrective responses. Changes in body state cause automatic physiological reactions as well as mental experiences — feelings — such as hunger, thirst, pain or fear. Evidence suggests that body state changes are mapped topographically in the CNS (specifically, in the upper brainstem and cerebral cortex). Changes recorded in these neural maps serve as triggers for physiological corrective responses and for interruption of those responses once the deviation has been rectified.

Feelings appear to have emerged, prevailed and mobilized such complex neural machinery because directly portraying the advantageous or disadvantageous nature of a physiologic situation as a 'felt experience' facilitates learning of the conditions responsible for homeostatic imbalances and of their respective corrections, as well as anticipation of future adverse or favourable conditions. In this way, feelings provide an additional level of regulation of behaviour.

From both evolutionary and ontogenetic perspectives, the experiential aspect of homeostatic neural mappings can also be considered the lowest level of the mind and consciousness. Indeed, the available evidence indicates that phylogenetically recent sectors of the nervous system, such as the cerebral cortex, contribute to but are not essential for the emergence of feelings, which are likely to arise instead from older regions such as the brainstem, suggesting that feelings are not exclusive to humans or even mammals.

Here, we outline a neural account for feelings by adopting an evolutionary perspective on their functional role and by drawing on systems-level evidence from human and non-human studies. We also venture that although feelings involve a systems level central process, they are rooted in events occurring at single-cell level, specifically in the unmyelinated axons conveying signals from humoral and visceral aspects of the body towards nuclei in the CNS.

Some of the most pressing health issues we face today, such as depression, drug addiction and intractable pain, are centred on pathologies of feeling. Elucidating the physiology of feeling states therefore has exceptional biomedical relevance.

Feelings reference physiological states

From antiquity to the present day, introspective analysis reported in philosophical writings, literary works and scientific observations reveals that descriptions of feelings tend to reference states of the body[1–5]. The repertoire of feelings includes thirst, food and air hunger (the urge to breathe), different kinds of pleasure and pain, disgust, fear, sadness and joy, as well as complex social responses such as contempt, shame, compassion and admiration[6–15]. By contrast, experiences related to exteroceptive senses (vision, hearing, touch, taste and smell) commonly cause emotions and ensuing feelings but are not feelings in and of themselves (see BOX 1 for the distinction between emotions and feelings). Whether feelings portray an internal state (for example, hunger or thirst) or are prompted by an external situation (for example, compassion or admiration), their dominant mental contents describe a state of the body in which the condition of the viscera (for example, heart, lungs, gut and skin) has a key role[1,2].

Seen in this light, it is reasonable to advance the idea that feelings, which are only accessible to the organism in which they occur, provide a subjective experiential window into the processes of life regulation. Feelings allow a glimpse into ongoing homeostatic regulation, ranging from basic processes such as metabolism to complex social emotions. This idea opens the way to envisioning neural mechanisms capable of generating feelings. William James[16] first proposed that feelings are derived from sensing our body states, and later work has supported the notion that a crucial requirement for the generation of feelings is the mapping of varied features of body state in the CNS[4,17–20]. This view has parallels with the accepted notion that visual and auditory experiences of objects in the outside world require neural maps of the features and location of those objects: for example, shapes, colour, textures, motion and position in space[21–28]. James focused on the cerebral cortex, but current evidence, as discussed below, shows that mappings begin at lower levels of the neuraxis. In brief, feelings require neural maps of body states. A number of physiological conditions must also be met for feelings to emerge from neural body maps. These conditions have not been fully identified but are likely to include features such as the intensity of the phenomena being mapped and the level of wakefulness.

The evolution of neural maps of the body

The availability of body state maps in the CNS is an obvious evolutionary advantage, as the centrally mapped body signals are related to physiological parameters and

Box 1 | **Key concepts in homeostatic regulation: drives, emotions and feelings**

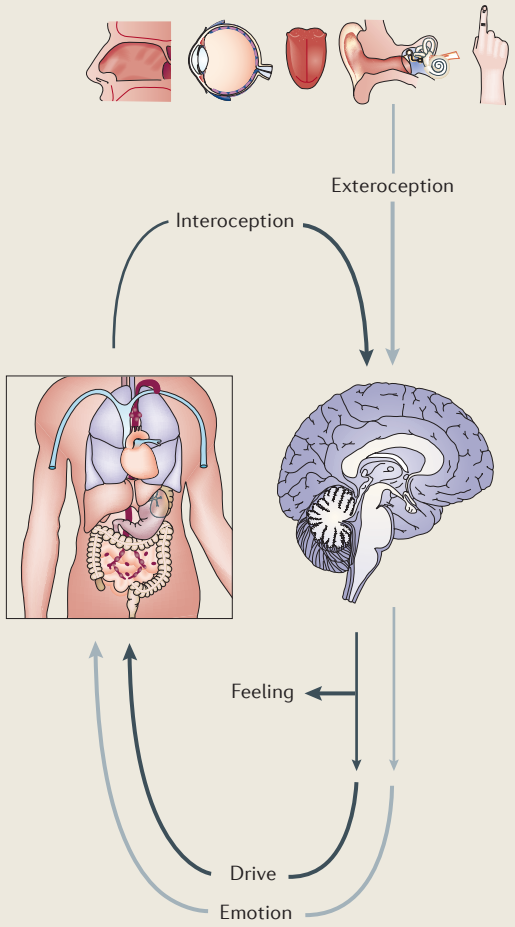
The CNS continually monitors our interior and exterior environments. Changes in the internal environment (for example, the degree of contraction of visceral muscles, heart rate, levels of metabolites in the internal milieu, and so on) are sensed by the interoceptive system[4], signalled to sensory regions of the CNS dedicated to body functions and displayed as neural maps of the body (interoceptive maps). Changes in the external environment are perceived via the exteroceptive senses (smell, taste, touch, hearing and sight) and displayed in dedicated sensory regions as neural maps of the external world (exteroceptive maps)[21–28] (see the figure).

Changes displayed in neural maps may trigger 'action programmes' — sets of innate, programmed physiological actions aimed at addressing the detected changes and thereby maintaining or restoring homeostatic balance. The actions include changes in viscera and internal milieu (for example, alterations in heart rate, breathing and hormonal secretion), striated muscle (for example, facial expressions and running) and cognition (for example, focusing attention and favouring certain ideas and modes of thinking). There are two main types of action programmes: 'drives' and 'emotions' (of note, some authors refer to all action programmes as emotions[42,43]). Drives are aimed at satisfying basic instinctual needs and include hunger, thirst, libido, exploration and play, care of progeny and attachment to mates[42,161,162]. In the case of thirst, the interoceptive detection and neural mapping of high blood osmolarity triggers a set of physiological actions that result in dryness of the mouth and an increase in urine concentration (see the table). Emotions include disgust, fear, anger, sadness, joy, shame, contempt, pride, compassion and admiration, and they are mostly triggered by the perception or recall of exteroceptive stimuli (although there are exceptions: for example, fear caused by interoceptive stimuli such as cardiac pain or air hunger)[163–166]. In the case of fear, the exteroceptive detection and mapping of an external threat (for example, a large animal) triggers physiological actions that include increased heart rate, secretion of adrenaline and the contraction of specific facial muscles, resulting in the facial expression of fear (see the table).

The changes in body state resulting from an action programme are in turn sensed by the interoceptive system and mapped in the CNS. Body state changes mapped in interoceptive neural maps may remain non-conscious or may be experienced consciously as 'feelings'.

Feelings are mental experiences that accompany a change in body state[17]. External changes displayed in the exteroceptive maps of vision or hearing are perceived but largely not felt directly in the sense of feeling we adopt in this text. However, they may lead to feelings indirectly by triggering an action programme that causes a change in body state and is subsequently felt.

Note that an action programme and the respective feeling are often referred to by the same name, although they are distinct phenomena. Thus 'fear' can refer to either an emotion (the set of programmed physiological actions triggered by a fear-inducing stimulus) or a feeling (the conscious experience of fear).



Stimulus	High blood osmolarity	Significant pressure against sharp object	Sight of a bear	Receiving bad news
Action programme (drive/ emotion)	• Dry mouth • Decreased water elimination • Irritability • Tiredness	• Retraction of affected limb or body part • Local vasodilation • Facial muscles form expression of pain • Attention focused on affected body part	• Increased heart and respiratory rates • Secretion of cortisol and adrenaline • Redistribution of blood flow • Analgesia • Facial muscles form expression of fear • Attention focused on perceived threat	• Increased blood pressure • Irregular heart rhythm • Decreased respiratory rate • Lacrimal secretion • Facial muscles form expression of sadness
Feeling	Thirst	Pain	Fear	Sadness

can be used to guide physiological corrections. In the event of a disturbance, both the magnitude and spatial location of the deviation can be instantly monitored, and the maps can be used both to trigger corrective actions, such as endocrine responses or emotive actions, and to suspend those corrections once equilibrium is regained. In the case of hunger, aspects of the state of satiety (for example, glycaemia) are constantly monitored and centrally represented. A physiological deviation (for example, hypoglycaemia) is sensed and centrally mapped, triggering corrective homeostatic changes (such as visceral motility and secretion, salivation, search for food, and so on). After feeding, the physiological deviations are corrected and the new parameters centrally mapped, triggering the suspension of the corrective measures[29–32].

From an evolutionary standpoint, the appearance of central maps of body states may have preceded the advent of the felt experiential aspect that defines feelings. This notion is supported by the finding that subjective, felt experience does not seem to be required in order for the maps to be used in the detection and correction of homeostatic imbalances. In fact, numerous disturbances are detected and dealt with

via action programmes or even simpler physiological mechanisms without an accompanying conscious experience, that is, a feeling. Examples of physiological processes that can occur subconsciously include regulation of heart rate, modulation of endocrine functions, adjustment of smooth muscle contraction, regulation of immunity, autonomic changes associated with the display of emotion-specific facial expressions, and even some aspects of facial recognition and decision-making[33–40]. Our hypothesis is that the addition of a felt experiential component to the basic somatic mapping emerged and prevailed in evolution because of the benefits it conferred on life regulation. Given that body states are necessarily valenced — they are either good or bad from the point of view of homeostasis — feelings are powerful proxies of ongoing biological value and natural guides of adaptive behaviour. Feelings along a range that includes pain and pleasure at its extremes force the organism to attend to its current conditions. Feelings also facilitate learning of the circumstances surrounding a change in body state and the subsequent application of this knowledge to the prediction of future situations, resulting in an increase in behavioural flexibility[5,41–43]. In brief, felt experiences permit more flexible and effective corrective measures than neural mapping alone, especially in the realm of complex behaviour[17,41].

Drives/emotions facilitate homeostasis

The immediate goals of homeostasis concern the management of life processes, including the governance of metabolism and the maintenance of somatic integrity via self-repair and defence[44]. Action programmes are instrumental for achieving these goals[45].

Action programmes do not require deliberation. They are instinctual — that is, biologically pre-set and largely stereotypical. For example, in the case of pressure from a sharp object, the ensuing action programmes include retraction of the affected area away from the stimulus and facial muscle contraction to form an expression of pain. However, their deployment can be influenced by learning (conditioning), which also allows the extension and transfer of homeostatic goals to objects and situations that become imbued with biological value: for example, money, power or drugs[46,47].

The action programme of fear provides another emblematic illustration of this process. The trigger for fear can be external (such as a threat) or internal (such as an evolving myocardial infarction or air hunger owing to oxygen restriction)[45,48]. The stimulus triggers a concert of responses, including preparatory actions (such as increased heart and respiratory rates, analgesia or the secretion of cortisol), freeze or flight behaviours (with immobility and impending motion, respectively, leading to different arrangements of blood flow) and attentional behaviours (leading to saliency of the causative object)[5,49–53].

From a bioengineering standpoint, the engagement of homeostatic action programmes requires four elements. First, a competent stimulus, such as an internal deviation from homeostatic range or an external object or circumstance, be it currently perceived or recalled in mind. Second, neural interfaces capable of detecting the stimulus. Third, neural execution sites capable of coordinating a collection of corrective actions — that is, the action programme (drive or emotion). And fourth, neural interfaces capable of detecting the completion of the correction and halting the corrective actions[5]. In summary, integrated neural maps of ongoing body states provide an effective neural interface for the detection of internal deviations from homeostatic range (stimuli), for the triggering of corrective responses (action programmes: drives and emotions), for determining when such corrective actions can be suspended and for generating the experiential component of the mapped body states (feelings).

The neural substrates of feeling

Neural processes can be studied at two main levels: macroscopic (the systems level, which is composed of general brain regions) and microscopic (neurons, synapses, glia and their molecular components). Thus, cognition can be analysed at the level of brain nuclei, regions or lobes, but its roots are ultimately found at the level of neuronal networks and the intricacies of synaptic signalling[21,54,55]. Similarly, it is conceivable that feelings also include both macro- and microscopic-level neural substrates[56]. There is remarkable evidence available regarding the macroscopic analysis of feeling states, and some preliminary proposals can be advanced. We therefore begin the search for the neural substrates of feelings at the level of macroscopic brain regions. The cellular basis of feelings, by contrast, is barely beginning to be approached. We discuss it in the last section.

Prior research in the mammalian brain has implicated a number of regions in the generation of drives and emotions that subsequently lead to feelings. These regions can be found at all levels of the neuraxis[57–60]. In the brainstem, for example, the following regions have been implicated: nucleus tractus solitarius (NTS); area postrema; parabrachial nucleus (PBN); ventral tegmental area (VTA); other monoamine nuclei; substantia nigra and the red nucleus; periaqueductal grey (PAG); the deep layers of the superior colliculus (SC); and the hypothalamus[5,42,61–63]. The intrinsic nature of these nuclei differs considerably, although they are all involved in generating corrective homeostatic actions. The PBN, NTS, PAG and SC display obvious topographic maps of body states[5,61,64–72], whereas the VTA, other monoamine-secreting nuclei and the substantia nigra do not appear

Glossary

Action programmes
A set of innate physiological actions triggered by changes in the internal or external environments and aimed at maintaining or restoring homeostatic balance. The actions include changes in viscera and internal milieu (for example, alterations in heart rate, breathing and hormonal secretion), striated muscle (for example, facial expressions and running) and cognition (for example, focusing attention and favouring certain ideas and modes of thinking). Action programmes include drives and emotions. Changes in body state resulting from an action programme are sensed by the interoceptive system, displayed in sensory maps of the body and may be experienced consciously as feelings.

Drive
An action programme that is aimed at satisfying a basic, instinctual physiological need. Examples include hunger, thirst, libido, exploration and play, care of progeny and attachment to mates.

Emotions
Action programmes largely triggered by external stimuli (perceived or recalled). Examples include disgust, fear, anger, sadness, joy, shame, contempt, pride, compassion and admiration.

Ephaptic transmission
Sideways interneuronal communication that is mediated by extracellular current flow.

Feelings
The mental experiences that accompany body states. Action programmes (drives and emotions) can elicit feelings. Experiences related to exteroceptive senses (vision, hearing, touch, taste and smell) commonly cause emotions and ensuing feelings but in general are not felt in and of themselves. This definition also excludes the use of 'feeling' in the sense of 'thinking' or 'intuiting'.

Homeostasis
The process of maintaining the internal milieu physiological parameters (such as temperature, pH and nutrient levels) of a biological system within the range that facilitates survival and optimal function.

Interoceptive system
A collection of nerve pathways and CNS nuclei dedicated to detecting and mapping homeostatic signals (such as degrees of visceral muscle contraction and internal milieu chemical composition). The main interoceptive pathways are the vagus nerve and the lamina I (spinothalamocortical) pathway. The interoceptive system monitors the state of the body, orchestrates responses thereto and has a central role in generating feelings.

to contain topographically organized information pertaining to the body. In keeping with the notion that feelings are likely to arise from maps of body states, it is sensible to focus the search for neural substrates of feelings on the regions exhibiting topographically organized somatic maps.

A set of structures located within the subcortical grey — including the amygdala, nucleus accumbens, ventral striatum, ventral pallidum and other basal ganglia and basal forebrain sectors — are involved in generating homeostatic actions, ranging from valence modulation (for example, taste hedonia in the nucleus accumbens[73]) to the triggering of motor behaviours (for example, fight or flight responses by the amygdaloid nuclei[49,52,53]). These regions do not appear to exhibit topographic maps. Thus, they may not have a direct role in generating feelings but instead may help shape the state of the body, for example via action programmes.

At the level of the cerebral cortex, several candidate structures need to be considered. The insular and somatosensory cortices (SI and SII) have fine-grain topographically organized maps of the body, and are thus likely to provide direct substrates of feeling[4,60,74]. The anterior cingulate cortices also exhibit a mapped organization, although their more noted function is the generation of actions. For example, motor responses to pain can be initiated in the anterior cingulate cortex[75–77].

In brief, the most prominent system level candidates for neural substrates of feelings can be found on two distinct phylogenetic levels: the more primitive level of the brainstem (specifically, the PBN, NTS, PAG and the deep layers of the SC) and the more recently evolved cerebral cortex (specifically, the insula, SI and SII) (FIG. 1).

The first-order integrated maps of interoceptive signals from the whole body are located in the brainstem. All of the prime candidates for the neural substrates of feelings as outlined above are regions concerned with interoception, which is the sense that continuously monitors the internal milieu and provides the CNS with real-time information on the state of the body. The main contributors to interoception are chemosensation, thermo-algic sensation (temperature and pain perception) and visceral sensation[4,61]. In addition, proprioception, the vestibular sense and light and non-discriminative ('limbic') touch may constitute additional interoceptive modalities[61,78]. The most prominent interoceptive pathways are the vagus nerve and the lamina I spinothalamocortical pathway (FIG. 1). The lamina I spinothalamocortical pathway is an afferent pathway conveying both thermo-algic and chemosensory information from most tissues of the body to the spinal cord (lamina I of the superficial dorsal horn) and brainstem (trigeminal nucleus)[4,79–84]. The vagus nerve, which is the main conduit for visceral sensation, carries signals pertaining to visceral states — especially from the cardiovascular, respiratory, gastrointestinal and genito-urinary systems — to the NTS in the lower brainstem[85–87]. Additional structures involved in interoception are the circumventricular organs. These are specialized structures that are involved in homeostatic functions, such as energy metabolism and water balance, and are positioned along the surface of the brain ventricles, where neurons make direct contact with the cerebrospinal fluid owing to the lack of a blood–brain barrier[88]. One such organ is the area postrema, a chemosensing nucleus adjacent to the NTS.

Interoceptive information gathered in the spinal cord and lower brainstem converges in higher brainstem regions, such as the PBN, the PAG and the reticular formation[4,61,89] (FIG. 1). The PBN, PAG and reticular formation are closely and bidirectionally interconnected[90–92]. Interoceptive information originating from different parts of the organism is continuously monitored and

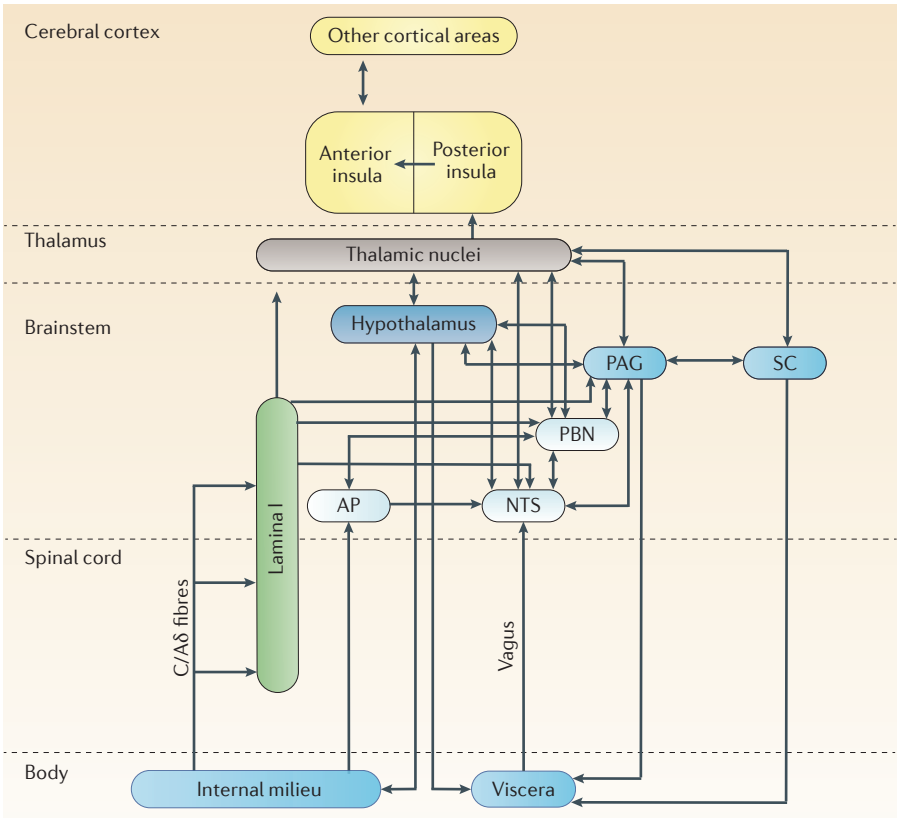


Figure 1 | **Interoceptive pathways and nuclei involved in sensing and mapping body states and generating feelings.** Two main pathways convey information from the internal milieu and viscera to the CNS. The lamina I pathway consists of C and Aδ fibres hailing from every area of the body and carrying information pertaining to muscle contraction in vessel walls, peripheral blood flow, temperature, pain, tissue injury, pH and the levels of O_2 and CO_2. This pathway converges in the lamina I (posterior horn of grey matter of the spinal cord and trigeminal nucleus). From here, secondary neurons ascend and project to homeostatic centres in the brainstem (nucleus tractus solitarius (NTS), parabrachial nucleus (PBN) and periaqueductal grey (PAG)). These centres are intimately interconnected and project to the cortex (chiefly the posterior insula) largely via the thalamus. Information collected in the posterior insula is projected rostrally to the anterior insula, which engages in crosstalk with other cortical areas (such as the orbitofrontal cortex). Some lamina I pathway fibres project to the insula directly (via the thalamus), bypassing the brainstem. The vagus nerve carries information from the viscera to the NTS, which then projects to the PBN, PAG and hypothalamus. Each of these structures also projects directly to the insular cortex via the thalamus. Extensive crosstalk between the lamina I and vagal pathways permits the formation of integrated maps of body states. The area postrema (AP) directly senses the internal milieu and is intimately connected to the NTS. SC, superior colliculus.

topographically mapped within these structures[61,64–67]. Thus, the upper brainstem (that is, the PBN and PAG) is the most caudal site at which different aspects of interoceptive afferent information can be assembled to form a whole-body, integrated map of body states. Such a map has a crucial role in life regulation and, in all likelihood, simultaneously provides a neural basis for the emergence of feeling states.

The SC warrants a special note. Although the role of its 'superficial' layers (layers I to III) in vision is well established[93], the 'deep' layers (layers IV to VII) have been relatively overlooked despite their physiological relevance. The deep layers of the SC receive inputs from different modalities (visual, auditory and somatosensory), resulting in three superposed topographic maps in a spatial register (that is, a region of one map corresponds to a specific region of the other two) so that there is correspondence between the information contained in all three maps[94–97]. This unique arrangement suggests that exteroceptive and interoceptive afferent information may first converge in the SC to form an integrated sensory map. The SC has been implicated in visual attention[98] and may also play an important part in processes of mind and self[42,99].

Feelings and the insula. Interoceptive information mapped in the brainstem is projected rostrally to the subcortical basal forebrain and to the cortical telencephalon, where it is remapped in the insula and somatosensory cortices SI and SII[4,17,58,84,100].

Contemporary neuroscience has identified the insula as the main cortical target for signals from the interoceptive system[4,58,60,101,102], and functional neuroimaging studies consistently implicate the human insula in both interoceptive and emotional feelings[58,60,84,100,103–110].

Recently, it has been proposed that the insula is not merely involved in human feelings but is their sole platform and, by extension, the critical provider of human awareness[60,111]. Several findings suggest that this hypothesis is problematic. First, given that several topographically organized nuclei of the upper brainstem, which are obligatory relay stations for most signals conveyed from the body to the insula, can produce elaborate representations of multiple parameters of body states, these regions should not be excluded a priori as platforms for feelings. Second, children born without cerebral cortex exhibit behaviours compatible with feeling states[112,113]. Third, bilateral insular damage does not abolish all feelings. Specifically, complete bilateral destruction of the insula as a result of herpes simplex encephalitis does not abolish either body or emotional feelings, including pain, pleasure, itch, tickle, happiness, sadness, apprehension, irritation, caring and compassion, in addition to hunger, thirst, and bladder and colon distension[114] (FIG. 2). In fact, feelings seem to dominate the mental landscape of patients with bilateral insular damage. Immediate comfort appears to be their main concern, fairly unbridled by cognitive constraints.

These observations do not support a view of the insula as a necessary substrate for feeling states. Thus, the generation of feelings must also rely on the brainstem and possibly on the SI and SII somatosensory cortices of the parietal lobe, which are spared in some patients that lack the insular cortices but remain fully capable of feeling[114]. Indeed, damage to the posterior half of the upper brainstem is associated with coma or vegetative state — two conditions in which feelings and sentience are abolished. The nuclei located in this sector include some of the structures that contain integrated somatosensory maps — the PBN, PAG and SC — as well as the reticular formation and some monoamine and acetylcholine nuclei. By contrast, lesions of the ventral half of the upper brainstem cause locked-in syndrome, in which feelings and consciousness (from sentience to autobiographical levels) are not abolished[17,115,116]. Neuroimaging studies also suggest a link between feelings and the brainstem, because inducing feelings triggers activation of brainstem structures[58,63]. Research involving experimental manipulation provides more compelling evidence for a role of subcortical structures. Decorticated mammals exhibit a remarkable persistence of coherent, goal-oriented behaviour that is consistent with feelings and consciousness[112]. Moreover, electrical stimulation of certain regions of the brainstem can elicit behavioural manifestations that are consistent with emotional responses in mammals. These responses are imbued with positive and negative valence in accordance with the type of emotion elicited and as determined by their effect on learning a simple task or the voluntary switching on or off of the stimulus by the animal[42,117]. Electrical stimulation of the brainstem can also elicit both emotions and the corresponding feelings in humans[118]. Together, these findings indicate a key role of the brainstem in triggering and supporting emotion and feeling.

Normal human feelings do not require the insula, although they consistently engage this region. To reconcile these observations requires the consideration that the larger maps of body state within the insula probably permit the assembling of finer-grain representations of interoceptive information than the maps assembled in the brainstem. In fact, some afferent information does appear to reach the insula directly, bypassing the brainstem[89]. Information that is present in the brainstem in implicit form may be explicitly represented in the insula according to body coordinates provided by SI and SII. Cortical re-mapping would allow finer discrimination of interoceptive states and permit a more precise modulation of the regulatory responses to an imbalance. In other words, insular maps would have more

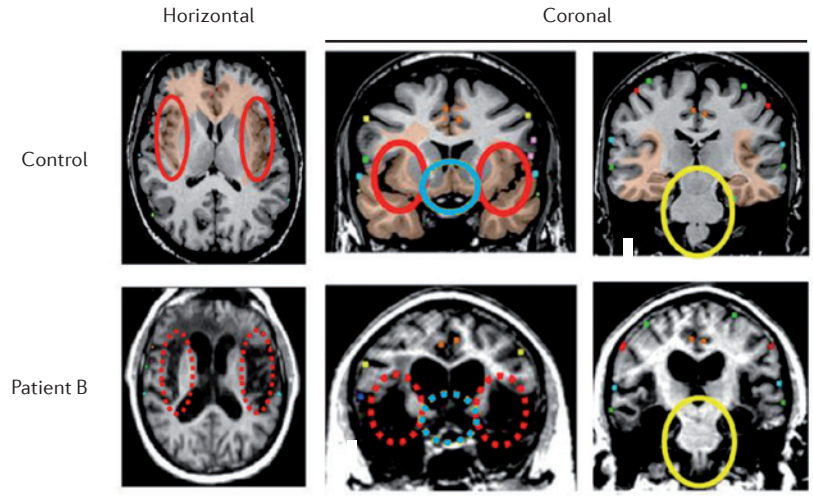


Figure 2 | **Patient B shows complete destruction of insular cortices in anatomical MRI scans.** Top row, control; bottom row, patient B. Red circles mark the insula; yellow circles mark the brainstem; blue circles mark the basal forebrain region. Data from REF. 114. Image courtesy of H. Damasio, University of Southern California, USA.

of a modulatory than a generative role in the processing and experience of body states. This is consistent with the finding that unilateral insular lesions diminish thermal and nociceptive discrimination[4,119,120], whereas even complete bilateral insular destruction does not abolish the ability to feel. Moreover, by virtue of its cortical location at the crossroads of numerous pathways involved in higher cognition, the insula makes extensive connections to cortical regions related to memory, language and reasoning. This suggests that although the insula is not necessary for experiencing feelings, it may be essential for the introduction of feelings into the flow of cognitive processes and thus facilitate the crosstalk between cognition and feeling. Such crosstalk may be necessary for the acquired rational control of drives and emotions, the absence of which would favour simpler behavioural patterns dominated by feeling states.

Feelings and the somatosensory cortex. With regard to the somatosensory cortices, both SI and SII can be functionally engaged during feelings[58,121,122], but damage to the somatosensory cortices has little or no effect on nociception and thermosensation[123]. Moreover, both rhesus monkeys and humans with bilateral parietal lesions (encompassing both SI and SII, albeit not in their entirety) exhibit behaviours clearly indicative of feeling states and display dramatic emotional lability[124,125]. Although further evidence from cases of complete, bilateral damage to both SI and SII is needed, the available evidence indicates that the somatosensory cortices are not necessary for the generation of body or emotional feelings. Instead, it is likely that these regions have a modulatory role in the experience of interoceptive body states, similar to that of the insula.

The evolution of feelings. Implicating subcortical regions such as the upper brainstem and hypothalamus in the generation of feelings has resounding evolutionary implications. Non-human mammals, birds, reptiles and even phylogenetically older species clearly display behaviours that are consistent with emotions and feelings[5,42,43,126]. Although there are dramatic differences between these species and humans at the level of the cerebral cortex, the evolutionarily older brainstem is essentially conserved in its layout, design and functions. It is therefore justifiable to propose that feelings are not exclusive to humans and that they have long been present in evolution[117]. Although it cannot at present be demonstrated that non-human species are capable of feeling, as feeling states are by definition subjective and accessible only to the organism in which they occur, there is no reason to assume otherwise. In fact, because many non-human species have all the neural substrates that are likely to be essential for the emergence of feeling, and exhibit behavioural manifestations that are consistent with feelings and emotion, the parsimonious assumption should be that feelings are present in these species. The sophisticated cognitive processes facilitated by the complex cerebral cortex of primates — such as memory, language, reasoning and imagination — probably contribute to more enriched and refined feeling states than those found in species with simpler nervous systems. Nonetheless, the fundamental elements of body state mapping, sentience and feelings imbued with valence are likely to be far older than our species, and probably even older than the advent of cerebral cortices. There is good reason to believe that the primate brain inherited the neural instruments for feeling from its ancestors and elaborated upon them.

The cellular basis of feelings

What are the cellular correlates of feelings? With rare exceptions, the issue has not been considered by the research community[5,54,56,127]. However, we believe this effort is imperative. The emergence of feelings requires the intricate interplay between its macro- and microscopic roots, both of which must be thoroughly elucidated if feelings and consciousness are to be fully understood.

With regard to the microscopic or cellular substrate for feeling states, we propose that: the crucial cells are to be found in the interoceptive system, specifically in the unmyelinated axons conveying signals from humoral and visceral aspects of the body towards nuclei in the spinal cord and brainstem. We also suggest that the ephaptic signalling that is likely to occur among such unmyelinated axons has an important role.

The processing of body signals largely relies on unmyelinated structures. The interoceptive pathways that are known to play a part in feeling states generally display very low levels of myelination. For example, the lamina I spinothalamocortical pathway is comprised of small-diameter, unmyelinated (C) and lightly myelinated (Aδ) fibres that are encased in Remak bundles, in which a single Schwann cell envelopes several axons[128]. Their conduction velocities are in the range of 1–8 ms^{-1}, as opposed to the well-myelinated Aα and Aβ fibres, which conduct exteroceptive signals at speeds of 14–60 ms^{-1} (REF. 129).

The vagus nerve, a principal conduit of fine visceral information, is also predominantly devoid of myelin. In mammals, including humans, approximately 80% of fibres in the main vagus trunk are unmyelinated[130,131], and most of the remaining 20% are poorly myelinated[132]. This predominance of unmyelinated fibres is even more dramatic in the vagal branches[133]. The vagus is unusual among the cranial nerves in its high content of unmyelinated fibres[134], and fibre arrangement within the vagus is also particular (whereas unmyelinated fibres in other cranial nerves tend to remain clustered in the periphery, in the vagus they appear evenly and uniformly distributed throughout the axonal substance[134]). Of note, unmyelinated fibres also mediate the affective aspects of touch[78,135]. The subset of C fibres related to this function operates as an additional component of the interoceptive system. In addition to the afferent interoceptive pathways, the central relays receiving these signals — the area postrema, NTS, PBN and PAG — are also poorly myelinated[136–138].

Given that the classically accepted evolutionary advantage of myelin sheaths is the acceleration of impulse propagation along the axon[139], one should question why the critical systems involved in homeostasis have remained largely unmyelinated. Myelination dramatically improves metabolic efficiency during axonal conduction, largely owing to a redistribution of ion channels — in myelinated fibres, these are concentrated in the nodes of Ranvier rather than equally distributed along the axon — and smaller ionic imbalances following nerve conduction[139,140]. However, owing to the metabolic price of generating and maintaining myelin sheaths, myelination may only be energetically profitable above a certain fibre diameter[141]. One possible explanation for the persistence of unmyelinated nerves is that only relatively thick fibres justify the metabolic cost of myelination, whereas fibres below a certain threshold remain unsheathed[142]. Another possibility is that conduction speed is essential for certain neural processes but not others, and the organism is willing to pay the metabolic cost of myelination only when necessary. However, this explanation implies that processes mediated by unmyelinated fibres, such as nociception and basic homeostasis, are not time-sensitive, whereas

common sense would indicate precisely the opposite. A third, often overlooked possibility is that myelin has pleiotropic effects, facilitating certain axonal functions but hindering others, thus rendering myelination advantageous for some neural processes and detrimental for others.

Some available evidence supports a pleiotropic role for myelin. Myelination increases conduction speed by means of insulation — that is, reducing ion exchange between the axon and its surroundings, thereby reducing electric current loss[139]. Consequently, any process relying on ionic exchanges would be hindered by myelination, whereas the unmyelinated fibres that mediate feelings allow free ionic exchanges. Although changes in membrane permeability are classically thought of as just a mechanism of nerve conduction leading to synaptic firing, growing evidence suggests that neuronal ionic exchanges may have other physiological roles. First, extracellular current flow is known to serve as a means for orthogonal (that is, transversal or sideways) neuronal communication, a process known as ephaptic transmission (as opposed to synaptic transmission, which works longitudinally). Ephaptic transmission has been reported both *in vitro* and *in vivo* and is thought to occur in the mammalian olfactory nerve, vagus nerve, peripheral nerves, spinal cord and in certain cortical areas[143,144]. Ephaptic communication may have a role in local synchronization of membrane potential across neurons[143]. In support of this view, extracellular potassium resulting from neuronal activation influences axonal excitability in neighbouring fibres[145]. Ephaptic communication is elicited ectopically upon myelin damage[146–148], suggesting that one of the consequences of myelin insulation is the blocking of ephaptic function — myelination inhibits ephaptic transmission both by acting as a direct physical obstacle to ionic exchanges and by increasing the distance between neighbouring axons[143].

A second illustration of the fact that neuronal ionic exchanges can be uncoupled from nerve conduction is that membrane potential can change dramatically without affecting action potentials[149]. In fact, membrane potential can be a better predictor of information transfer from afferent stimuli[150], and even of animal behaviour[149], than action potentials themselves. Subthreshold potentials may also mediate aspects of olfactory coding[151].

That myelin blocks neuronal membrane permeability and is largely absent in the interoceptive pathways that sense body states and underlie feelings suggests a link between neuronal membrane permeability and the sensing of body states that leads to feelings. Along these lines, it has been suggested that the extensive vulnerability of the neuron to its extracellular environment underlies the cellular basis of sentience[127].

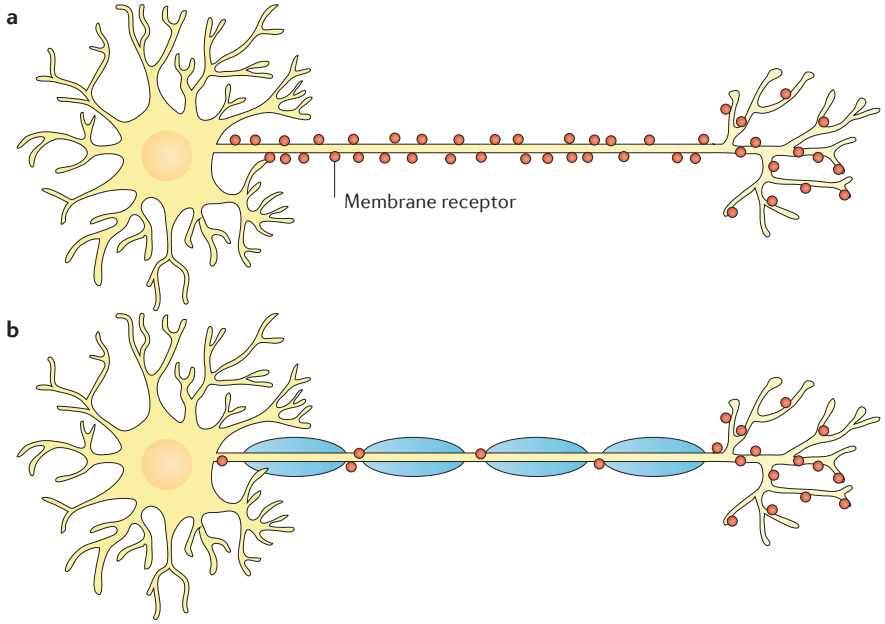


Figure 3 | **Axonal membrane receptors in unmyelinated and myelinated fibres.** An illustration of the increased surface area of unmyelinated axons available for sampling the local environmental milieu. **a** | Because an important role of interoceptive fibres is to sense circulating factors and the internal milieu, axonal trunks with an extensive chemosensitive surface area would significantly increase the sensitivity of a fibre. Red dots on axons symbolize membrane receptors for circulating ligands. **b** | By contrast, myelin insulation would block direct access of circulating factors.

Myelin may also hinder interoception by directly blocking the binding of ligands to membrane receptors in interoceptive fibres (FIG. 3). Certain unmyelinated fibres (for example, in the vagus nerve) can be activated by chemostimulation not only in peripheral nerve terminals but also along the axonal length, which is known as the axonal trunk. Membrane receptors for several molecules that play a part in interoception — ATP, serotonin, acetylcholine and capsaicin — are found in the trunk of these fibres[152–157]. Chemosensitive axonal trunks make evolutionary sense in fibres dedicated to sensing circulating factors and the internal milieu, a central mechanism of interoception. If each axon was chemosensitive only at its terminals rather than along the full axonal length, far more nerve fibres, or at least ramifications thereof, would be required to cover all areas of the organism. Presumably, myelin insulation would reduce chemosensitivity along the axon by physically impeding the access of circulating ligands to membrane receptors.

In brief, myelin accelerates axonal conduction, but it also blocks the neuronal membrane from its surroundings, hindering both ionic exchanges and binding of circulating ligands to membrane receptors. We therefore suggest that evolutionary pressure may have selected for myelination when conduction speed is the main concern — for example, in pathways involved in motor control and higher cognition — and against myelination when membrane access (either by ions involved in neuronal electric current or by receptor ligands) is more important — for example, in pathways involved in interoception and feelings.

From sentience to feelings. How does the cellular proto-phenomenon — sentience — become a systems level feeling? A model commonly accepted for cognition is that synaptic firing at the single-neuron level is amplified, via temporal synchronization, into a systems level phenomenon[158,159]. The same process could conceivably be applied to feelings[54,127]. Changes at the cellular level would temporally synchronize across many individual neurons (for example, via ephaptic communication), ultimately contributing to the experience of feelings. According to this model, minor changes in visceral function or internal milieu composition (such as local concentration of oxygen, CO_2 and

glucose) would trigger membrane ionic exchanges in a small number of local interoceptive fibres, whereas stronger deviations would affect proportionally larger numbers of fibres. Signals conveyed by these activated fibres converge on the interoceptive monitoring centres of the spinal cord and brainstem. The number of afferent fibres from the same topographic location firing simultaneously would represent a measure of stimulus intensity[160] that, when interpreted in the context of the neural maps of the body, may constitute a fine-tuned code for determining which corrective actions, if any, would be warranted. For example: subtle stimuli would recruit few, if any, axons and elicit minimal or no corrections; stimuli of intermediate intensity would affect a substantial number of fibres and trigger autonomic corrective measures; and major disturbances would recruit a large number of axons and elicit not only autonomic corrections but also become consciously perceived (via a feeling), leaving room for voluntary behavioural adaptation.

Concluding remarks

A crucial characteristic of feelings is their intrinsic valence — the direction, positive or negative, and the intensity of the homeostatic deviations proxied by feelings — which helps to explain why the organism follows the orientation provided by a feeling. Interestingly, exteroceptive processes that in all likelihood evolved later (for example, vision and hearing) do not contain intrinsic valence, although they are commonly labelled with valences generated from body states. Thus, higher cognition borrows the labels first developed as a component of homeostatic regulation.

The advent of feelings was simultaneously the advent of the mind. Early organisms capable of feeling were, for the first time in evolution and unlike all other life forms, aware of some aspects of their own existence[117]. Feelings paved the way for the establishment of higher levels of cognition and consciousness, culminating in the modern human mind. Accordingly, shedding light on the underpinnings of feeling is likely to provide insights into consciousness and the mind.

The elucidation of feeling states also has prominent biomedical relevance. Some of the most devastating medical and public health problems of our time — depression, substance addiction and intractable pain — are centred on pathologies of feeling. Depression alone is the leading cause of disease in the United States and the leading cause of non-infectious disease worldwide. The mechanism for these pathologies is not understood and the available therapies are widely regarded as unsatisfactory. Insight into the neurophysiology of feelings may lead to the development of more effective treatments for this class of disorders.

Antonio Damasio and Gil B. Carvalho are at the Brain and Creativity Institute, University of Southern California, 3620 A McClintock Avenue, Suite 265, Los Angeles, California 90089-2921, USA.

Correspondence to A.D. e-mail: damasio@usc.edu

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1. Plato. *Symposium* (Kessinger, 2010).
2. Heaton, K. W. Body-conscious Shakespeare: sensory disturbances in troubled characters. *Med. Humanit.* **37**, 97–102 (2011).
3. Morrisj, J. S. How do you feel? *Trends Cogn. Sci.* **6**, 317–319 (2002).
4. Craig, A. D. How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Rev. Neurosci.* **3**, 655–666 (2002).
5. Damasio, A. *Self Comes to Mind: Constructing the Conscious Brain* (Pantheon, 2010; Vintage, 2011).
6. Ortony, A. & Turner, T. J. What's basic about basic emotions? *Psychol. Rev.* **97**, 315–331 (1990).
7. Sorensen, L. B., Moller, P., Flint, A., Martens, M. & Raben, A. Effect of sensory perception of foods on appetite and food intake: a review of studies on humans. *Int. J. Obes.* **27**, 1152–1166 (2003).
8. DeWall, C. N. & Baumeister, R. F. Alone but feeling no pain: effects of social exclusion on physical pain tolerance and pain threshold, affective forecasting, and interpersonal empathy. *J. Pers. Soc. Psychol.* **91**, 1–15 (2006).
9. Frijda, N. H., Kuipers, P. & ter Schure, E. Relations among emotion, appraisal, and emotional action readiness. *J. Pers. Soc. Psychol.* **57**, 212–228 (1989).
10. Wicker, B. *et al.* Both of us disgusted in *my* insula: the common neural basis of seeing and feeling disgust. *Neuron* **40**, 655–664 (2003).
11. Schnall, S., Haidt, J., Clore, G. L. & Jordan, A. H. Disgust as embodied moral judgment. *Pers. Soc. Psychol. Bull.* **34**, 1096–1109 (2008).
12. Goetz, J. L., Keltner, D. & Simon-Thomas, E. Compassion: an evolutionary analysis and empirical review. *Psychol. Bull.* **136**, 351–374 (2010).
13. Keltner, D., Ellsworth, P. C. & Edwards, K. Beyond simple pessimism: effects of sadness and anger on social perception. *J. Pers Soc. Psychol.* **64**, 740–752 (1993).
14. Algoe, S. B. & Haidt, J. Witnessing excellence in action: the 'other-praising' emotions of elevation, gratitude, and admiration. *J. Posit. Psychol.* **4**, 105–127 (2009).
15. Kringelbach, M. L. & Berridge, K. C. *Pleasures of the Brain* (Oxford Univ. Press, 2009).
16. James, W. *The Principles of Psychology* (Henry Holt and Company, 1890).
17. Damasio, A. *The Feeling of What Happens: Body and Emotion in the Making of Consciousness* (Harcourt, 1999).
18. Hohmann, G. W. Some effects of spinal cord lesions on experienced emotional feelings. *Psychophysiology* **3**, 143–156 (1966).
19. Wiens, S., Mezzacappa, E. S. & Katkin, E. S. Heartbeat detection and the experience of emotions. *Cogn. Emotion* **14**, 417–427 (2000).
20. Montoya, P. & Schandry, R. Emotional experience and heartbeat perception in patients with spinal cord injury and control subjects. *J. Psychophysiol.* **8**, 289–296 (1994).
21. Kandel, E. R., Schwartz, J. H. & Jessell, T. M., Siegelbaum, S. A. & Hudspeth, A. J. *Principles of Neural Science* 5th edn (The McGraw-Hill Companies, 2012).
22. Kobatake, E. & Tanaka, K. Neuronal selectivities to complex object features in the ventral visual pathway of the macaque cerebral cortex. *J. Neurophysiol.* **71**, 856–867 (2012).
23. Gao, X. W., Podladchikova, L., Shaposhnikov, D., Hong, K. & Shevtsova, N. Recognition of traffic signs based on their colour and shape features extracted using human vision models. *J. Vis. Commun. Image R.* **17**, 675–685 (2006).
24. Lowe, D. G. Object recognition from local scale-invariant features. in *Proc. of the Seventh IEEE International Conference on Computer Vision* Vol. 2 1150–1157 (IEEE, 1999).
25. Allman, J. M. & Kaas, J. H. A representation of the visual field in the caudal third of the middle tempral gyrus of the owl monkey (*Aotus trivirgatus*). *Brain Res.* **31**, 85–105 (1971).
26. Evans, E. F., Ross, H. F. & Whitfield, I. C. The spatial distribution of unit characteristic frequency in the primary auditory cortex of the cat. *J. Physiol.* **179**, 238–247 (1965).
27. Roe, A. W., Pallas, S. L., Hahm, J. O. & Sur, M. A map of visual space induced in primary auditory cortex. *Science* **250**, 818–820 (1990).
28. Udin, S. B. & Fawcett, J. W. Formation of topographic maps. *Annu. Rev. Neurosci.* **11**, 289–327 (1988).
29. Taylor, L. A. & Rachman, S. J. The effects of blood sugar level changes on cognitive function, affective state, and somatic symptoms. *J. Behav. Med.* **11**, 279–291 (1988).
30. Scammell, T. E. & Winrow, C. J. Orexin receptors: pharmacology and therapeutic opportunities. *Annu. Rev. Pharmacol. Toxicol.* **51**, 243–266 (2011).
31. Wardle, J. Hunger and satiety: a multidimensional assessment of responses to caloric loads. *Physiol. Behav.* **40**, 577–582 (1987).
32. Monello, L. F. & Mayer, J. Hunger and satiety sensations in men, women, boys, and girls. *Am. J. Clin. Nutr.* **20**, 253–261 (1967).
33. Czura, C. J. & Tracey, K. J. Autonomic neural regulation of immunity. *J. Intern. Med.* **257**, 156–166 (2005).
34. Bauer, R. M. Autonomic recognition of names and faces in prosopagnosia: a neuropsychological application of the Guilty Knowledge Test. *Neuropsychologia* **22**, 457–469 (1984).
35. Craig, A. D. A new view of pain as a homeostatic emotion. *Trends Neurosci.* **26**, 303–307 (2003).
36. Porges, S. W. Neuroception: a subconscious system for detecting threats and safety. *Zero Three* **24**, 19–24 (2004).
37. Ekman, P., Levenson, R. W. & Friesen, W. V. Autonomic nervous system activity distinguishes among emotions. *Science* **221**, 1208–1210 (1983).
38. Bechara, A., Damasio, H., Tranel, D. & Damasio, A. R. Deciding advantageously before knowing the advantageous strategy. *Science* **275**, 1293–1295 (1997).
39. Gabella, G. *Encyclopedia of Life Sciences* (John Wiley & Sons, 2001).
40. Tranel, D. & Damasio, A. R. Knowledge without awareness: an autonomic index of facial recognition by prosopagnosics. *Science* **228**, 1453–1454 (1985).
41. Damasio, A. *Looking for Spinoza: Joy, Sorrow, and the Feeling Brain* (Harcourt, 2003).
42. Panksepp, J. *Affective Neuroscience: The Foundations of Human and Animal Emotions* (Oxford Univ. Press, 1998).
43. Denton, D. A. *The Primordial Emotions: The Dawning of Consciousness* (Oxford Univ. Press, 2005).
44. Cannon, W. B. *The Wisdom of the Body.* (W. W. Norton & Co, 1932).
45. Damasio, A. Neural basis of emotions. *Scholarpedia* **6**, 1804 (2011).
46. Wright, R. *The Moral Animal: The New Science of Evolutionary Psychology* (Pantheon/Vintage, 1994).
47. Sanabria, F. Tools, drugs, and signals in the road from evolution to money. *Behav. Brain Sci.* **29**, 193–194 (2012).
48. Feinstein, J. S., Adolphs, R., Damasio, A. & Tranel, D. The human amygdala and the induction and experience of fear. *Curr. Biol.* **21**, 34–38 (2011).
49. Blair, R. J. Neurocognitive models of aggression, the antisocial personality disorders, and psychopathy. *J. Neurol. Neurosurg. Psychiatry* **71**, 727–731 (2001).
50. Fanselow, M. S. Conditioned fear-induced opiate analgesia: a competing motivational state theory of stress analgesia. *Ann. NY Acad. Sci.* **467**, 40–54 (1986).
51. Kalin, N. H., Shelton, S. E. & Davidson, R. J. The role of the central nucleus of the amygdala in mediating fear and anxiety in the primate. *J. Neurosci.* **24**, 5506–5515 (2004).
52. Adolphs, R., Tranel, D., Damasio, H. & Damasio, A. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature* **372**, 669–672 (1994).
53. LeDoux, J. E. Emotion: clues from the brain. *Annu. Rev. Psychol.* **46**, 209–235 (1995).
54. Maclennan, B. Protophenomena and their neurodynamical correlates. *J. Conscious. Stud.* **3**, 409–424 (1996).
55. Crick, F. H. C. *The Astonishing Hypothesis: The Scientific Search for the Soul* (Charles Scribner's Sons, 1994).

56. Llinás, R. R. *I of the Vortex: From Neurons to Self* (MIT Press, 2001).
57. Pessoa, L. How do emotion and motivation direct executive control? *Trends Cogn. Sci.* **13**, 160–166 (2009).
58. Damasio, A. *et al.* Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neurosci.* **3**, 1049–1056 (2000).
59. Lang, P. J. & Davis, M. Emotion, motivation, and the brain: reflex foundations in animal and human research. *Prog. Brain Res.* **156**, 3–29 (2006).
60. Craig, A. D. How do you feel — now? The anterior insula and human awareness. *Nature Rev. Neurosci.* **10**, 59–70 (2009).
61. Parvizi, J. & Damasio, A. Consciousness and the brainstem. *Cognition* **79**, 135–160 (2001).
62. Risold, P. Y., Thompson, R. H. & Swanson, L. W. The structural organization of connections between hypothalamus and cerebral cortex. *Brain Res. Brain Res. Rev.* **24**, 197–254 (1997).
63. Buhle, J. T. *et al.* Common representation of pain and negative emotion in the midbrain periaqueductal gray. *Soc. Cogn. Affect. Neurosci.* 24 Mar 2012 (doi:10.1093/scan/nss038).
64. Farkas, E., Jansen, A. S. & Loewy, A. D. Periaqueductal gray matter projection to vagal preganglionic neurons and the nucleus tractus solitarius. *Brain Res.* **764**, 257–261 (1997).
65. Hamilton, B. L. Projections of the nuclei of the periaqueductal gray matter in the cat. *J. Comp. Neurol.* **152**, 45–58 (1973).
66. Herbert, H. & Saper, C. B. Cholecystokinin-, galanin-, and corticotropin-releasing factor-like immunoreactive projections from the nucleus of the solitary tract to the parabrachial nucleus in the rat. *J. Comp. Neurol.* **293**, 581–598 (1990).
67. Herbert, H., Moga, M. M. & Saper, C. B. Connections of the parabrachial nucleus with the nucleus of the solitary tract and the medullary reticular formation in the rat. *J. Comp. Neurol.* **293**, 540–580 (1990).
68. Bester, H., Besson, J. M. & Bernard, J. F. Organization of efferent projections from the parabrachial area to the hypothalamus: a *Phaseolus vulgaris*-leucoagglutinin study in the rat. *J. Comp. Neurol.* **383**, 245–281 (1997).
69. Ricardo, J. A. & Koh, E. T. Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. *Brain Res.* **153**, 1–26 (1978).
70. Cameron, O. G. Interoception: the inside story—a model for psychosomatic processes. *Psychosom. Med.* **63**, 697–710 (2001).
71. Keay, K. A., Clement, C. I., Owler, B., Depaulis, A. & Bandler, R. Convergence of deep somatic and visceral nociceptive information onto a discrete ventrolateral midbrain periaqueductal gray region. *Neuroscience* **61**, 727–732 (1994).
72. Rinaman, L. Interoceptive stress activates glucagon-like peptide-1 neurons that project to the hypothalamus. *Am. J. Physiol.* **277**, R582–R590 (1999).
73. Berridge, K. C. & Robinson, T. E. Parsing reward. *Trends Neurosci.* **26**, 507–513 (2003).
74. Damasio, A. *Descartes' Error: Emotion, Reason, and the Human Brain* (Penguin, 2005).
75. Rainville, P., Duncan, G. H., Price, D. D., Carrier, B. & Bushnell, M. C. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* **277**, 968–971 (1997).
76. Dum, R. P., Levinthal, D. J. & Strick, P. L. The spinothalamic system targets motor and sensory areas in the cerebral cortex of monkeys. *J. Neurosci.* **29**, 14223–14235 (2009).
77. Shackman, A. J. *et al.* The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature Rev. Neurosci.* **12**, 154–167 (2011).
78. Olausson, H. *et al.* Unmyelinated tactile afferents signal touch and project to insular cortex. *Nature Neurosci.* **5**, 900–904 (2002).
79. Craig, A. D. A new version of the thalamic disinhibition hypothesis of central pain. *Pain Forum* **7**, 1–14 (1998).
80. Craig, A. D. Propriospinal input to thoracolumbar sympathetic nuclei from cervical and lumbar lamina I neurons in the cat and the monkey. *J. Comp. Neurol.* **331**, 517–530 (1993).
81. Craig, A. D. Distribution of brainstem projections from spinal lamina I neurons in the cat and the monkey. *J. Comp. Neurol.* **361**, 225–248 (1995).
82. Craig, A. D. An ascending general homeostatic afferent pathway originating in lamina I. *Prog. Brain Res.* **107**, 225–242 (1996).
83. Craig, A. D. The functional anatomy of lamina I and its role in post-stroke central pain. *Prog. Brain Res.* **129**, 137–151 (2000).
84. Craig, A. D., Chen, K., Bandy, D. & Reiman, E. M. Thermosensory activation of insular cortex. *Nature Neurosci.* **3**, 184–190 (2000).
85. Beckstead, R. M. & Norgren, R. An autoradiographic examination of the central distribution of the trigeminal, facial, glossopharyngeal, and vagal nerves in the monkey. *J. Comp. Neurol.* **184**, 455–472 (1979).
86. Kalia, M. & Mesulam, M. M. Brain stem projections of sensory and motor components of the vagus complex in the cat: I. The cervical vagus and nodose ganglion. *J. Comp. Neurol.* **193**, 435–465 (1980).
87. Kalia, M. & Mesulam, M. M. Brain stem projections of sensory and motor components of the vagus complex in the cat: II. Laryngeal, tracheobronchial, pulmonary, cardiac, and gastrointestinal branches. *J. Comp. Neurol.* **193**, 467–508 (1980).
88. Shapiro, R. E. & Miselis, R. R. The central neural connections of the area postrema of the rat. *J. Comp. Neurol.* **234**, 344–364 (1985).
89. Klop, E. M., Mouton, L. J., Hulsebosch, R., Boers, J. & Holstege, G. In cat four times as many lamina I neurons project to the parabrachial nuclei and twice as many to the periaqueductal gray as to the thalamus. Neuroscience **134**, 189–197 (2005).
90. Krukoff, T. L., Harris, K. H. & Jhamandas, J. H. Efferent projections from the parabrachial nucleus demonstrated with the anterograde tracer *Phaseolus vulgaris* leucoagglutinin. *Brain Res. Bull.* **30**, 163–172 (1993).
91. Mantyh, P. W. Connections of midbrain periaqueductal gray in the monkey. II. Descending efferent projections. *J. Neurophysiol.* **49**, 582–594 (1983).
92. Karimnamazi, H. & Travers, J. B. Differential projections from gustatory responsive regions of the parabrachial nucleus to the medulla and forebrain. *Brain Res.* **813**, 283–302 (1998).
93. Klier, E. M., Wang, H. & Crawford, J. D. The superior colliculus encodes gaze commands in retinal coordinates. *Nature Neurosci.* **4**, 627–632 (2001).
94. Stein, B. E. Development of the superior colliculus. *Annu. Rev. Neurosci.* **7**, 95–125 (1984).
95. Huerta, M. F. & Harting, J. K. Connectional organization of the superior colliculus. *Trends Neurosci.* **7**, 286–289 (1984).
96. May, P. J. The mammalian superior colliculus: laminar structure and connections. *Prog. Brain Res.* **151**, 321–378 (2006).
97. Wurtz, R. H. & Albano, J. E. Visual-motor function of the primate superior colliculus. *Annu. Rev. Neurosci.* **3**, 189–226 (1980).
98. Zenon, A. & Krauzlis, R. J. Attention deficits without cortical neuronal deficits. *Nature* **489**, 434–437 (2012).
99. Strehler, B. L. Where is the self? A neuroanatomical theory of consciousness. *Synapse* **7**, 44–91 (1991).
100. Brooks, J. C. Nurmikko, T. J., Bimson, W. E., Singh, K. D. & Roberts, N. fMRI of thermal pain: effects of stimulus laterality and attention. *Neuroimage* **15**, 293–301 (2002).
101. Mesulam, M. M. & Mufson, E. J. Insula of the old world monkey. I. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. *J. Comp. Neurol.* **212**, 1–22 (1982).
102. Mufson, E. J. & Mesulam, M. M. Insula of the old world monkey. II: Afferent cortical input and comments on the claustrum. *J. Comp. Neurol.* **212**, 23–37 (1982).
103. Critchley, H. D., Wiens, S., Rotshtein, P., Ohman, A. & Dolan, R. J. Neural systems supporting interoceptive awareness. *Nature Neurosci.* **7**, 189–195 (2004).
104. Stephan, E. *et al.* Functional neuroimaging of gastric distention. *J. Gastrointest. Surg.* **7**, 740–749 (2003).
105. Phillips, M. L. *et al.* The effect of negative emotional context on neural and behavioural responses to oesophageal stimulation. *Brain* **126**, 669–684 (2003).
106. Kong, J. *et al.* Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity. *Hum. Brain Mapp.* **27**, 715–721 (2006).
107. Singer, T. *et al.* Empathy for pain involves the affective but not sensory components of pain. *Science* **303**, 1157–1162 (2004).
108. Henderson, L. A., Gandevia, S. C. & Macefield, V. G. Somatotopic organization of the processing of muscle and cutaneous pain in the left and right insula cortex: a single-trial fMRI study. *Pain* **128**, 20–30 (2007).
109. Hennenlotter, A. *et al.* A common neural basis for receptive and expressive communication of pleasant facial affect. *Neuroimage* **26**, 581–591 (2005).
110. Jabbi, M., Swart, M. & Keysers, C. Empathy for positive and negative emotions in the gustatory cortex. *Neuroimage* **34**, 1744–1753 (2007).
111. Craig, A. D. Significance of the insula for the evolution of human awareness of feelings from the body. *Ann. NY Acad. Sci.* **1225**, 72–82 (2011).
112. Merker, B. Consciousness without a cerebral cortex: a challenge for neuroscience and medicine. *Behav. Brain Sci.* **30**, 63–81 (2007).
113. Shewmon, D. A., Holmes, G. L. & Byrne, P. A. Consciousness in congenitally decorticate children: developmental vegetative state as self-fulfilling prophecy. *Dev. Med. Child Neurol.* **41**, 364–374 (1999).
114. Damasio, A., Damasio, H. & Tranel, D. Persistence of feelings and sentience after bilateral damage of the insula. *Cereb. Cortex* 3 Apr 2012 (doi:10.1093/cercor/bhs077).
115. Plum, F. & Posner, J. B. *The Diagnosis of Stupor and Coma (Contemporary Neurology Vol.10)* (Oxford Univ. Press, 1972).
116. Parvizi, J. & Damasio, A. R. Neuroanatomical correlates of brainstem coma. *Brain* **126**, 1524–1536 (2003).
117. Panksepp, J. The basic emotional circuits of mammalian brains: do animals have affective lives? *Neurosci. Biobehav Rev.* **35**, 1791–1804 (2011).
118. Bejjani, B. P. *et al.* Transient acute depression induced by high-frequency deep-brain stimulation. *N. Engl. J. Med.* **340**, 1476–1480 (1999).
119. Schmahmann, J. D. & Leifer, D. Parietal pseudothalamic pain syndrome. Clinical features and anatomic correlates. *Arch. Neurol.* **49**, 1032–1037 (1992).
120. Greenspan, J. D. & Winfield, J. A. Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum. *Pain* **50**, 29–39 (1992).
121. Harrison, N. A., Gray, M. A., Gianaros, P. J. & Critchley, H. D. The embodiment of emotional feelings in the brain. *J. Neurosci.* **30**, 12878–12884 (2010).
122. Piche, M., Arsenault, M. & Rainville, P. Dissection of perceptual, motor and autonomic components of brain activity evoked by noxious stimulation. *Pain* **149**, 453–462 (2010).
123. Head, H. & Holmes, G. Sensory disturbances from cerebral lesions. *Brain* **34**, 102–254 (1911).
124. Mori, E. & Yamadori, A. Rejection behaviour: a human homologue of the abnormal behaviour of Denny-Brown and Chambers' monkey with bilateral parietal ablation. *J. Neurol. Neurosurg. Psychiatry* **52**, 1260–1266 (1989).
125. Denny-Brown, D. & Chambers, R. A. The parietal lobe and behavior. *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* **36**, 35–117 (1958).
126. Steiner, J. E., Glaser, D., Hawilo, M. E. & Berridge, K. C. Comparative expression of hedonic impact: affective reactions to taste by human infants and other primates. *Neurosci. Biobehav. Rev.* **25**, 53–74 (2001).
127. Cook, N. D. The neuron-level phenomena underlying cognition and consciousness: synaptic activity and the action potential. *Neuroscience* **153**, 556–570 (2008).
128. Murinson, B. B. & Griffin, J. W. C-fiber structure varies with location in peripheral nerve. *J. Neuropathol. Exp. Neurol.* **63**, 246–254 (2004).
129. Harper, A. A. & Lawson, S. N. Conduction velocity is related to morphological cell type in rat dorsal root ganglion neurones. *J. Physiol.* **359**, 31–46 (1985).
130. Foley, J. O. & DuBois, F. S. Quantitative studies of the vagus nerve in the cat. I. The ratio of sensory to motor fibers. *J. Comp. Neurol.* **67**, 49–67 (2004).
131. Hoffman, H. H. & Schnitzlein, H. N. The numbers of nerve fibers in the vagus nerve of man. *Anat. Rec.* **139**, 429–435 (1961).
132. Friede, R. L. & Samorajski, T. Relation between the number of myelin lamellae and axon circumference in fibers of vagus and sciatic nerves of mice. *J. Comp. Neurol.* **130**, 223–231 (1967).
133. Prechtl, J. C. & Powley, T. L. The fiber composition of the abdominal vagus of the rat. *Anat. Embryol. (Berl.)* **181**, 101–115 (1990).
134. Koch, S. L. The structure of the third, fourth, fifth, sixth, ninth, eleventh and twelfth cranial nerves. *J. Comp. Neurol.* **26**, 541–552 (1916).
135. Vallbo, A. B., Olausson, H. & Wessberg, J. Unmyelinated afferents constitute a second system coding tactile stimuli of the human hairy skin. *J. Neurophysiol.* **81**, 2753–2763 (1999).

136. Mantyh, P. W. The midbrain periaqueductal gray in the rat, cat, and monkey: a Nissl, Weil, and Golgi analysis. *J. Comp. Neurol.* **204**, 349–363 (1982).
137. Miller, A. J., McKoon, M., Pinneau, M. & Silverstein, R. Postnatal synaptic development of the rat. *Brain Res.* **284**, 205–213 (1983).
138. Leslie, R. A. Comparative aspects of the area postrema: fine-structural considerations help to determine its function. *Cell. Mol. Neurobiol.* **6**, 95–120 (1986).
139. Hartline, D. K. & Colman, D. R. Rapid conduction and the evolution of giant axons and myelinated fibers. *Curr. Biol.* **17**, R29–R35 (2007).
140. Waxman, S. G. Conduction in myelinated, unmyelinated, and demyelinated fibers. *Arch. Neurol.* **34**, 585–589 (1977).
141. Harris, J. J. & Attwell, D. The energetics of CNS white matter. *J. Neurosci.* **32**, 356–371 (2012).
142. Lee, S. *et al.* A culture system to study oligodendrocyte myelination processes using engineered nanofibers. *Nature Methods* **9**, 917–922 (2012).
143. Bokil, H., Laaris, N., Blinder, K., Ennis, M. & Keller, A. Ephaptic interactions in the mammalian olfactory system. *J. Neurosci.* **21**, RC173 (2001).
144. Meyer, R. A., Raja, S. N. & Campbell, J. N. Coupling of action potential activity between unmyelinated fibers in the peripheral nerve of monkey. *Science* **227**, 184–187 (1985).
145. Eng, D. L. & Kocsis, J. D. Activity-dependent changes in extracellular potassium and excitability in turtle olfactory nerve. *J. Neurophysiol.* **57**, 740–754 (1987).
146. Kamermans, M. & Fahrenfort, I. Ephaptic interactions within a chemical synapse: hemichannel-mediated ephaptic inhibition in the retina. *Curr. Opin. Neurobiol.* **14**, 531–541 (2004).
147. Moller, A. R. Hemifacial spasm: ephaptic transmission or hyperexcitability of the facial motor nucleus? *Exp. Neurol.* **98**, 110–119 (1987).
148. Rasminsky, M. Ephaptic transmission between single nerve fibres in the spinal nerve roots of dystrophic mice. *J. Physiol.* **305**, 151–169 (1980).
149. Crochet, S. & Petersen, C. C. Correlating whisker behavior with membrane potential in barrel cortex of awake mice. *Nature Neurosci.* **9**, 608–610 (2006).
150. Aur, D. Connolly, C. I. & Jog, M. S. Computing information in neural spikes. *Neural Process. Lett.* **23**, 183–199 (2006).
151. Pearce, T., Verschure, P., White, J. & Kauer, J. Robust stimulus encoding in olfactory processing: hyperacuity and efficient signal transmission. *Lect. Notes Comput. Sci.* **2036**, 461–479 (2001).
152. Cockayne, D. A. *et al.* Urinary bladder hyporeflexia and reduced pain-related behaviour in $P2X_5$-deficient mice. *Nature* **407**, 1011–1015 (2000).
153. Lang, P. M. *et al.* Characterization of neuronal nicotinic acetylcholine receptors in the membrane of unmyelinated human C-fiber axons by *in vitro* studies. *J. Neurophysiol.* **90**, 3295–3303 (2003).
154. Lang, P. M., Tracey, D. J., Irnich, D., Sippel, W. & Grafe, P. Activation of adenosine and P2Y receptors by ATP in human peripheral nerve. *Naunyn Schmiedebergs Arch. Pharmacol.* **366**, 449–457 (2002).
155. Irnich, D., Tracey, D. J., Polten, J., Burgstahler, R. & Grafe, P. ATP stimulates peripheral axons in human, rat and mouse — differential involvement of A_{2B} adenosine and P2X purinergic receptors. *Neuroscience* **110**, 123–129 (2002).
156. Lang, P. M., Moalem-Taylor, G., Tracey, D. J., Bostock, H. & Grafe, P. Activity-dependent modulation of axonal excitability in unmyelinated peripheral rat nerve fibers by the $5\text{-}HT_3$ serotonin receptor. *J. Neurophysiol.* **96**, 2963–2971 (2006).
157. Lang, P. M. & Grafe, P. Chemosensitivity of unmyelinated axons in isolated human gastric vagus nerve. *Auton. Neurosci.* **136**, 100–104 (2007).
158. Engel, A. K., Fries, P., Konig, P., Brecht, M. & Singer, W. Temporal binding, binocular rivalry, and consciousness. *Consci. Cogn.* **8**, 128–151 (1999).
159. Singer, W. Neuronal synchrony: a versatile code for the definition of relations? *Neuron* **24**, 49–65, 111–125 (1999).
160. Gybels, J., Handwerker, H. O. & Van Hees, J. A comparison between the discharges of human nociceptive nerve fibres and the subject's ratings of his sensations. *J. Physiol.* **292**, 193–206 (1979).
161. Maslow, A. H. A theory of human motivation. *Psychol. Rev.* **50**, 370–396 (1943).
162. Berridge, K. C. Motivation concepts in behavioral neuroscience. *Physiol. Behav.* **81**, 179–209 (2004).
163. Immordino-Yang, M. H., McColl, A., Damasio, H. & Damasio, A. Neural correlates of admiration and compassion. *Proc. Natl Acad. Sci. USA* **106**, 8021–8026 (2012).
164. Keltner, D & Buswell, B. N. Evidence for the distinctness of embarrassment, shame, and guilt: a study of recalled antecedents and facial expressions of emotion. *Cogn. Emot.* **10**, 155–172 (1996).
165. Ekman, P. & Friesen, W. V. Constants across cultures in the face and emotion. *J. Pers Soc. Psychol.* **17**, 124–129 (1971).
166. LeDoux, J. E. *The Emotional Brain: The Mysterious Underpinnings of Emotional Life* (Simon & Schuster, 1996).

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Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION
Antonio Damasio's homepage: www.usc.edu/schools/college/bci

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