OPINION

How do you feel — now? The anterior insula and human awareness

A. D. (Bud) Craig

Abstract | The anterior insular cortex (AIC) is implicated in a wide range of conditions and behaviours, from bowel distension and orgasm, to cigarette craving and maternal love, to decision making and sudden insight. Its function in the re-representation of interoception offers one possible basis for its involvement in all subjective feelings. New findings suggest a fundamental role for the AIC (and the von Economo neurons it contains) in awareness, and thus it needs to be considered as a potential neural correlate of consciousness.

In a 2002 Perspective article I discussed the phylogenetically new primate lamina I spinothalamocortical pathway, which provides a primary interoceptive representation of the physiological condition of the body in the posterior insular cortex[1]. The evidence at that time indicated that the anterior insular cortex (AIC) (FIG. 1) contains interoceptive re-representations that substantialize (that is, provide the basis for) all subjective feelings from the body and perhaps emotional awareness, consistent with the essence of the James–Lange theory of emotion and Damasio's 'somatic marker' hypothesis. Studies in diverse fields now offer a wealth of convergent data that support and extend these proposals. In this Perspective, I discuss recent functional-imaging reports that describe activation of the AIC and highlight those that seem the most important for understanding its role. The available evidence suggests strongly that the AIC has a fundamental role in human awareness. After discussing this concept, I describe a model that could explain how the AIC might play this role.

Recent findings of AIC activation

The recent imaging studies that report activation of the AIC are here categorized in different fields of inquiry (FIG. 2). Selected studies are highlighted and others are listed in Supplementary information S1 (table). In most but not all of these studies, the AIC and the anterior cingulate cortex (ACC) are jointly activated, consistent with the idea that they serve as complementary limbic sensory and motor regions that work together, similar to the somatosensory and motor cortices (BOX 1). The studies that reported activation of the AIC but not the ACC are explicitly noted. In addition, activation in the AIC often spills over into the frontal operculum and the neighbouring inferior frontal gyrus (IFG), and it overlies the distribution of von Economo neurons (VENs) in this 'fronto-insular' junction (BOX 2).

Interoception. Interoceptive stimuli that have been shown to activate the AIC include thirst, dyspnea, 'air hunger', the Valsalva manoeuvre, sensual touch, itch, penile stimulation, sexual arousal, coolness, warmth, exercise, heartbeat, wine-tasting (in sommeliers), and distension of the bladder, stomach, rectum or oesophagus (see Supplementary information S1 (table)). Our original positron emission tomography (PET) study showed that objective cool temperatures are represented linearly in the contralateral dorsal posterior insula, whereas subjective ratings of these stimuli correlate with activation of the contralateral mid-insula and then most strongly with the AIC and the adjacent orbitofrontal cortex on the right side[2], suggestive of a posterior-to-mid-to-anterior pattern of integration of interoceptive information. Here, I highlight three reports that substantiate and expand these findings.

Critchley *et al.* reported functional MRI (fMRI) and morphometric data indicating a specific role for the right AIC in heartbeat awareness[3], an interoceptive measure that correlates with individual subjective emotional awareness[4]. A PET study of non-painful gastric distension reported that a subjective sense of fullness was associated with activation peaks in the bilateral dorsal posterior insula, the left mid-insula, the left AIC and the ACC[5]; these results conform to the posterior-to-mid-to-anterior pattern of integration mentioned above, but the left-sided asymmetry seems to correlate with the fact that this stimulus activates primarily vagal (parasympathetic) afferents (BOX 3). Finally, activation was observed in the bilateral AIC (right side (R)>left side (L)) during non-painful oesophageal distention or viewing of fearful faces, and such activation displayed synergistic enhancement when these stimuli were delivered simultaneously[6], suggesting that emotional states are integrated with interoceptive states in the representation of the subjective feelings of the moment.

Pain is a significant interoceptive feeling, and four recent pain studies are noteworthy here. One study reported that noxious heat stimulation of the left or right hand activated the contralateral dorsal posterior insula, the bilateral mid-insula (R>L) and, when the subject attended to the stimulus, the right AIC (R>>L)[7]. Another study reported that the objective intensity of a heat pain stimulus correlated with activation in the posterior insula, whereas the subjective evaluation of heat pain correlated with activation in the bilateral AIC (R>L)[8]. A different study found that empathic feelings for a loved one receiving painful simulation were associated with activation of the bilateral AIC but not the posterior insula[9]. Finally, investigators injected volunteers with hypertonic saline in the arm and the leg to produce a painful stimulation of muscle or the overlying skin, and they observed distinct, neighbouring sites of activation in the AIC that were somatotopically arranged[10].

Awareness of body movement. Two reports[11,12] showed that the feeling of agency or awareness of body control during hand movements is associated with activation

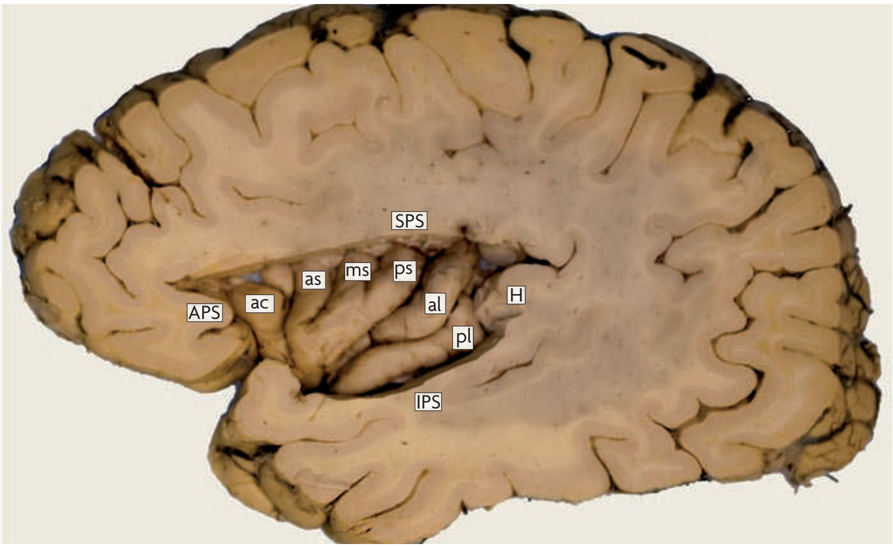


Figure 1 | **Anatomy of the insula.** A photograph of the left insular cortex of a human patient. For a comparison with the insulae of other patients, see REF. 114. The human insular cortex is a distinct but hidden lobe of the brain. It is disproportionately (~30%) enlarged in the human relative to the macaque monkey[109]. It has 5–7 oblique gyri, but its morphology is quite variable, even between the two sides[114–118]. A comprehensive hodological description in the macaque is lacking, and few connectivity analyses of the insula have been made in humans. Primary interoceptive representations are located in the dorsal posterior insula and re-represented in a polymodal integrative zone in the mid-insula and again in the anterior insular cortex (AIC)[2,7,119,120]. The primary interoceptive, gustatory and vagal representations extend to the anterior limit of the insula in macaques but only to the middle of the insula in humans[98,121–124], which suggests that the AIC of humans has no equivalent in the monkey. The most anterior and ventral (inferior) portion of the human insula that adjoins the frontal operculum is probably the most recently evolved, because this part (as well as the anterior cingulate cortex; BOX 1) contains von Economo neurons (BOX 2). as, anterior short insular gyrus; al, anterior long insular gyrus; ac, accessory gyrus; APS, anterior peri-insular sulcus; H, Heschl's gyrus; IPS, inferior peri-insular sulcus; ms, middle short insular gyrus; ps, posterior short insular gyrus; pl, posterior long insular gyrus; SPS, superior peri-insular sulcus. Photograph is courtesy of Professor Thomas P. Naidich, Mount Sinai Medical Center, New York.

in the bilateral mid-insula. Another study reported activation in the right mid-insula during the rubber-hand illusion, in which the subject was not actually moving but felt like the moving hand was their own[13]. The authors suggested that the mid-insula activation during movement might represent a sense of body ownership rather than agency. No activation was observed in the ACC in these studies. Finally, a recent study reported that simply hearing the piano notes that a subject has just learned to play activates the same mid-insular region[14]. Based on a meta-analysis that they performed of prior studies, the authors proposed that the insula contains a sensorimotor map that represents movements. My interpretation of these studies is that the insular cortex contains a somatotopic representation of the subjective feelings of one's current movements as part of a representation of all feelings from the body.

Self-recognition. The imaging studies cited in Supplementary information S1 (table) reported that the act of seeing one's own image produced activation in the AIC. The most recent study[15] contrasted brain activation in subjects viewing photos of their own face or body with activation when these subjects viewed photos of a close colleague or scrambled images. During both types of visual self-recognition the authors found selective activation of the AIC and the adjacent IFG and ACC, all on the right side. They suggested that the right AIC and ACC "could give rise to an abstract representation of oneself that could possibly participate in maintaining a sense of self".

Vocalization and music. There are differing views on the involvement of the insula in speech (some authors include the insula in Broca's area), as summarized in the reviews cited in Supplementary information S1 (table), but there is consistent evidence for the involvement of the AIC in music. Of note, a PET study reported findings that differentiated brain regions associated with familiarity, pitch, rhythm and timbre in music listening; the authors reported robust activation specifically in the left AIC (not the ACC) during the rhythm task (in which occasional notes in well-known melodies were mis-timed)[16]. A recent fMRI study compared activation induced by listening to pleasant and unpleasant music that the subjects selected individually and found that subjectively pleasant music induced activation of the AIC that was greater on the left than on the right side[17]. One review presented evidence that the AIC is activated bilaterally during overt speech and singing and, strikingly, that the AIC activation is asymmetric during covert singing: activity in the right AIC was higher during slow tempos (<3 Hz); activity in the left AIC was higher during fast tempos (>3 Hz)[18].

Emotional awareness. Almost all recent imaging studies of emotion report joint activation of the AIC and the ACC in subjects experiencing emotional feelings, including maternal and romantic love, anger, fear, sadness, happiness, sexual arousal, disgust, aversion, unfairness, inequity, indignation, uncertainty, disbelief, social exclusion, trust, empathy, sculptural beauty, a 'state of union with God', and a hallucinogenic state (induced by ayahuasca). Thus, the AIC is activated not just in association with subjective feelings from the body, but apparently with all subjective feelings. One noteworthy study examined resting-state functional connectivity and found two networks: an 'executive control' network that included the dorsolateral prefrontal cortex (DLPFC) and parietal areas, and an emotional 'salience' network that included the bilateral AIC, the ACC, the amygdala and the hypothalamus[19]. Significantly, small regions in the left AIC and the medial prefrontal cortex (MPFC) near the ACC were included in both networks, suggesting a basis for both emotional awareness of cognitive functions and the influence of emotion on cognition. In addition, several studies (for example, REFS 20,21) found selective activation in overlapping regions in the AIC during an empathic feeling and a comparable subjective feeling (for example, seeing disgust expressed on another's face and smelling a disgusting odour, respectively), with the former located anterior to the latter (consistent with the posterior-to-anterior gradient towards greater behavioural complexity in the frontal cortex[22]). Notably, similar locations in the AIC may be active during quite different emotions and behaviours[20,21,23]; across all studies, a main determinant of location in the AIC seems to be the region of somatic association, with face representations located most anterior and hand and foot representations located more posterior (see also REF. 14).

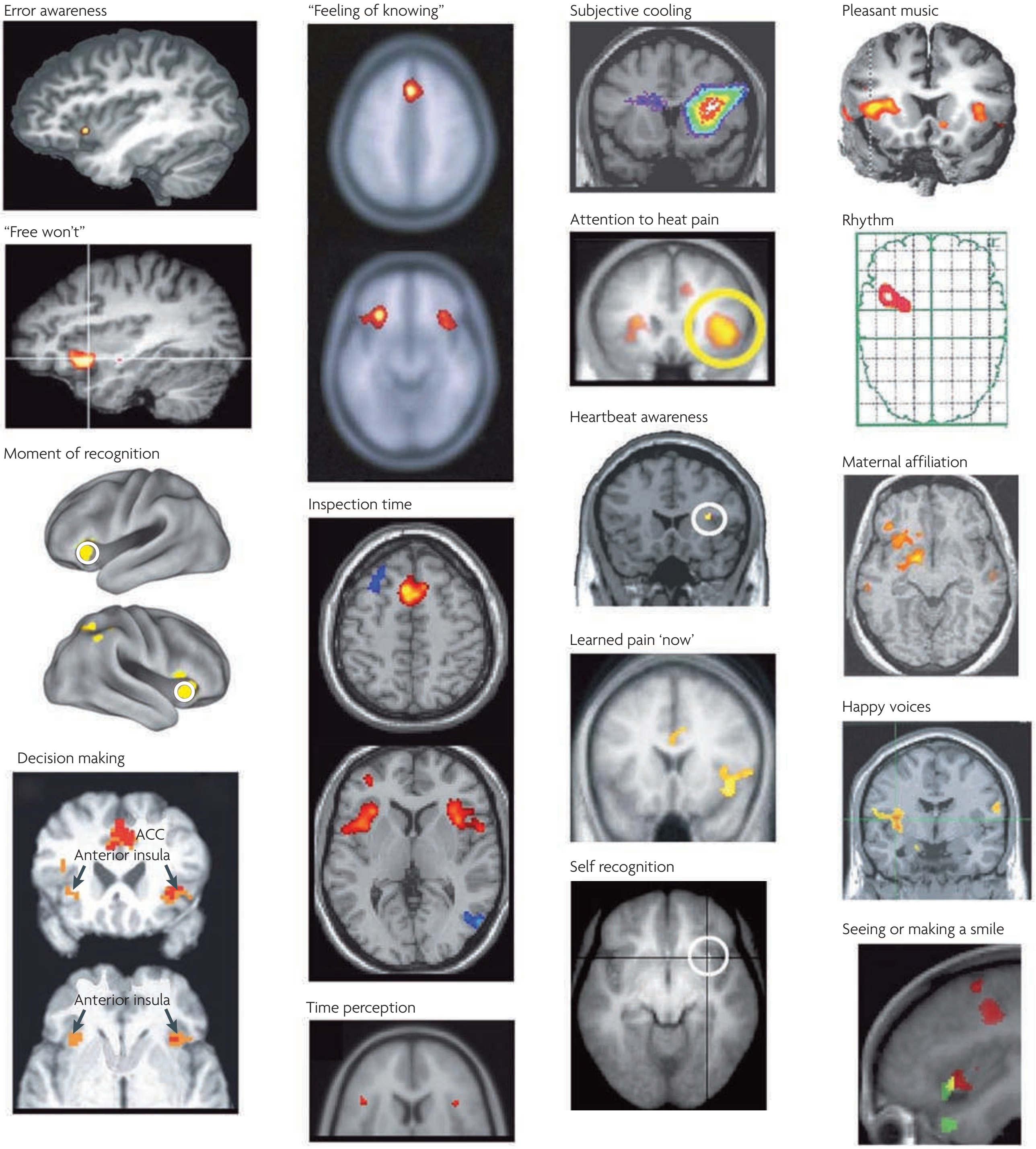
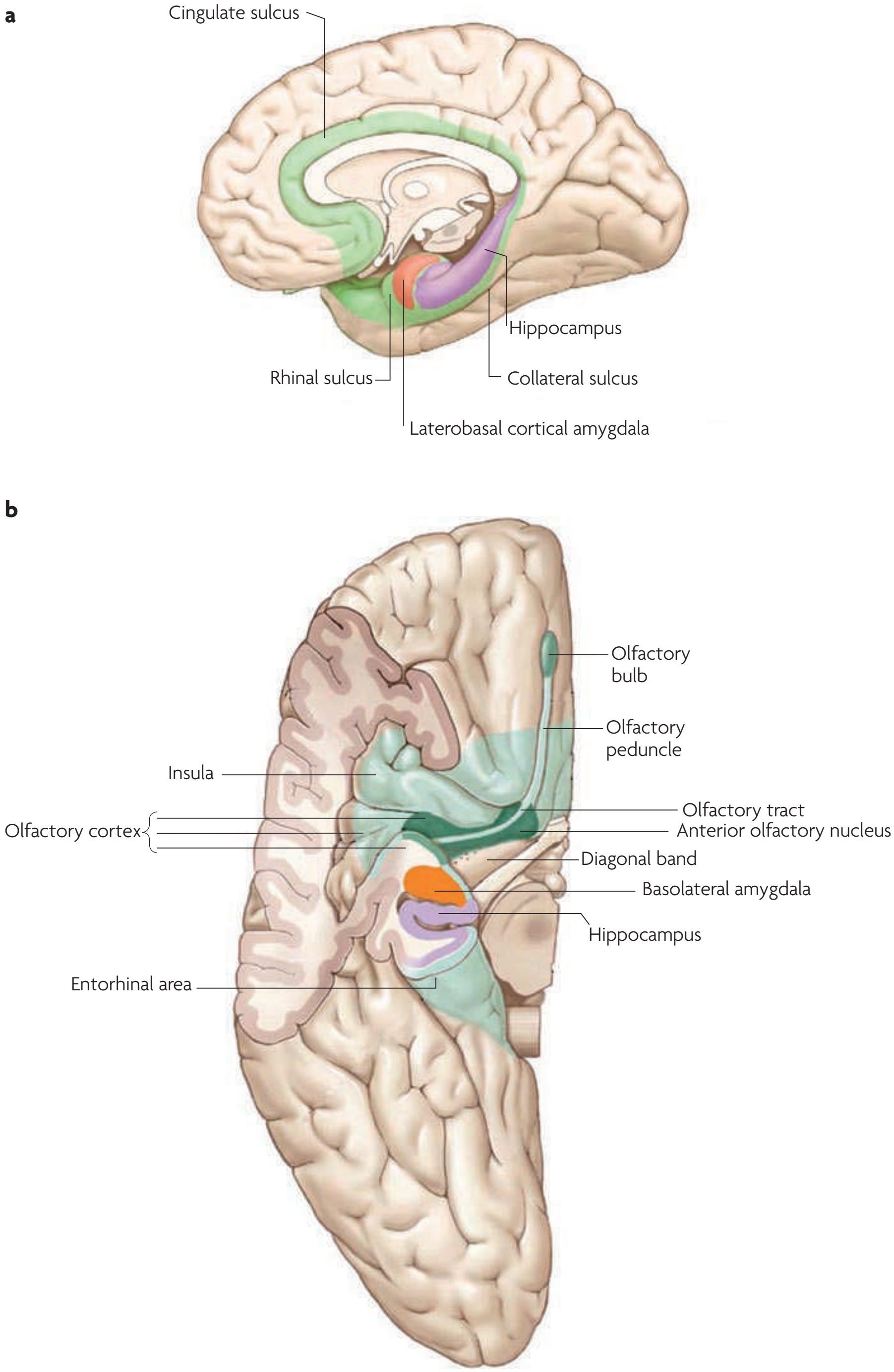


Figure 2 | **Activation of the AIC.** A summary of imaging results showing activation of the anterior insular cortex (AIC) during particular tasks and emotions highlighted in the text. The two right-hand columns contain images from different studies that found predominantly unilateral activation; images in the two left-hand columns show mostly bilateral activation. Stimuli that activate the right AIC are generally arousing to the body (for example, pain). The left AIC is activated mainly by positive and affiliative emotional feelings (BOX 3). For example, activation of the left AIC was reported in mothers viewing photos of their own child[125]; greater activation of the left than of the right AIC was associated with both maternal and romantic love[126]; activation of the left AIC was reported while subjects were either seeing or making a smile[21]; activation of the left AIC was found while subjects attended to happy voices[127]; activation of the left AIC was associated with hearing pleasant music[17]; selective activation of the left AIC was observed in subjects experiencing joy[128]; and selective activation of the left AIC in females was found that correlated with self-reported orgasm ratings[129]. ACC, anterior cingulate cortex. Images are reproduced, with permission, from (in order from top to bottom and left to right): (first column) REF. 23 © (2007) Elsevier, REF. 45 © (2007) Society for Neuroscience, REF. 39 © (2007) Society for Neuroscience, REF. 40 © (2007) Society for Neuroscience; (second column), REF. 41 © (2002) Cell Press, REF. 31 © (2004) Elsevier, REF. 34 © (2007) Elsevier; (third column) REF. 2 © (2000) Macmillan Publishers Ltd (all rights reserved), REF. 7 © (2002) Elsevier, REF. 3 © (2004) Macmillan Publishers Ltd (all rights reserved), REF. 24 © (2004) Macmillan Publishers Ltd (all rights reserved), REF. 15 © (2007) Elsevier; (fourth column) REF. 17 © (2006) Wiley, REF. 16 © (1997) Oxford Journals, REF. 125 © (2004) Elsevier, REF. 127 © (2006) Oxford Journals, REF. 20 © (2005) Elsevier.

Box 1 | The co-activation of the AIC and the ACC

It is understandably mystifying that a region of the ventrolateral prefrontal cortex (the anterior insular cortex (AIC)) and a region of the medial prefrontal cortex (the anterior cingulate cortex (ACC)) are co-active in so many behaviours, because such widely separated regions in the cortex generally have distinct roles. The insular cortex was long regarded simply as a visceral sensory region, based on findings by Penfield, Mesulam and Saper[84–86], whereas the medial prefrontal cortex has been associated with conflict responses, impulsive behaviour and autonomic activity. In an earlier article I suggested that the insula and the ACC be regarded as limbic sensory and motor cortices that respectively engender the feeling and the motivation (agency) that constitute any emotion[1]. This suggestion was based on the dual lamina I spinothalamocortical projection to both the insula and the ACC, the co-activation of these areas in virtually all studies of emotion, their respective descending projections to sensory (parabrachial nucleus) and motor (periaqueductal grey) brainstem regions, the overall anatomical organization of the frontal cortex into sensory and motor networks, and the evolutionarily ancient limbic role of the cingulate cortex in integrated behavioural control. I regarded the AIC as the probable site for awareness on the basis of its afferent representation of the 'feelings' from the body, and the ACC as the probable site for the initiation of behaviours. A recent review[87] offered support for this view and an explanation for the anatomical separation of the insula and the ACC. The ACC evolved first as a motor-control region aligned with the sensory integration, in the hippocampus and the amygdala, of olfactory-guided group behaviour in mammals. The insula evolved later for cortical processing of homeostatic sensory activity in the individual animal. The two regions naturally became linked for integrative autonomic control, and in mammalian evolution the insula grew as limbic behavioural activity became aligned more with autonomic activity than with olfactory activity. This anatomical perspective[87] is illustrated in the ventral view of the brain in the figure, which reveals the common relationship of these structures to the olfactory epithelium. Figure is reproduced, with permission, from REF. 87 © (1999) Elsevier.



Risk, uncertainty and anticipation. Of the articles listed in Supplementary information S1 (table), I note particularly one report that 'emotional value' in the immediate present, as specified in a second-order temporal-difference model of learning, correlated selectively with activity in the right AIC[24]; another study (in which this learning model was adapted for neuroeconomic studies) reported that both the risk-prediction signals and the risk-prediction error signals specified in the model were present only in the bilateral AIC[25]. No activation was observed in the ACC in this study. Activation in the AIC is also correlated with feelings of anticipated value during purchase and sales decisions[26].

Visual and auditory awareness of the moment. Several reports that associated activation in the AIC with awareness of sensory bistable percepts must be explicitly noted here[27–29], but I highlight three additional studies. The first is a PET study which found that the right AIC and the ACC are sensitive to cross-modal sensory time synchronization and display a graded response to a mismatch in timing between auditory and visual stimuli that should normally be synchronous (for example, a speaking mouth)[30]. The second is an fMRI study that examined

Box 2 | **VENs and awareness**

An extraordinary morphological characteristic of the anterior insular cortex (AIC) and the anterior cingulate cortex (ACC) in hominoid primates is the unique concentration of clusters of large spindle-shaped neurons among the pyramidal neurons in layer 5, called von Economo neurons (VENs) after an early neuroanatomist[88,89]. Their connections are not known, but I have proposed[78] that VENs are the substrate for fast interconnections between the physically separated advanced limbic sensory (the AIC) and motor (the ACC) cortices. Analogous to the tight interconnections between the contiguous somatosensory and motor cortices (so-called U-fibres) needed for manual dexterity (for example, for playing a musical instrument), the VENs might enable fast, highly integrated representations of emotional moments and behaviours. They may underlie the joint activity in the AIC and the ACC reported in most studies. The loss of emotional awareness and self-conscious behaviours in patients with frontotemporal dementia that correlates with the degeneration of VENs directly supports this notion[75,76,90,91].

Hof, Allman and colleagues reported that many VENs are present in aged humans, but progressively fewer are found in infants, gorillas, bonobos and chimpanzees, and they are not present at all in macaque monkeys[88,89]. This clear phylogenetic progression parallels the results of the mirror test for self-awareness[2,55]. VENs have recently been reported in elephants[92] and whales[93]. The possibility that this implies sentience in these animals received support recently when elephants were reported to pass the mirror test[94]. Interestingly, there are reports that elephants sing or make music communally (as captured in a film on the National Geographic website), which would be consistent with the present model for awareness, in which music (viewed as a rhythmic temporal progression of emotionally laden moments) is an emergent property of awareness. By contrast, although most people feel that particular dogs and cats have some sense of awareness, the cortex of these animals receives an integrated brainstem homeostatic pathway and only a primordial homologue of the ascending lamina I pathway that underlies the emergence of interoceptive re-representations in the AIC of humanoid primates[1]. Whether that is a sufficient basis for sentience is unresolved: cats and dogs do not pass the mirror test, and a lesion of the presumptive homologous pathway in cats does not produce the same devastating effects on interoception that it produces in humans[1]. Rats and lizards apparently do not have a homologous anatomical substrate at all[1].

“inspection time” using a briefly displayed asymmetric visual test stimulus (a one-sided fork) followed immediately by an ambiguous stimulus (so-called backward masking)[31]. The authors reported that subjects’ performance in detecting the asymmetry decreased progressively from 100% to chance levels for presentation times shorter than 150 ms, yet activation in the AIC and the ACC selectively and progressively increased with shorter presentation times. The authors inferred from these data an “effort-related process” that guides goal-directed attention, which they related to psychometric intelligence; however, this observation can also be interpreted as evidence for a role for the AIC and ACC in heightened awareness of the immediate moment. The third study[32] used the attentional-blink paradigm, in which a second target cannot be perceived if it occurs too soon after a primary target in a rapid series of visual stimuli. The authors reported joint activation of the AIC/IFG and the ACC (plus activation of the DLPFC and parietal regions) when the second target was correctly detected at the shortest intervals (100–200 ms) but not when it was not perceived. They suggested that the AIC/IFG and the ACC might contain a “conceptual short-term memory buffer prone to decay and replacement by other stimuli” that receives processed input from a parietal network and requires a finite period of time to transfer information into working memory (in the DLPFC).

Time perception. Joint activation of the AIC and the ACC or nearby areas has been reported in many studies of ‘mental time-keeping’ and interval estimation across the range of seconds to sub-seconds, but little explanation has been given for this activity (for example, see REF. 33). In a recent report, task difficulty was manipulated in order to isolate time estimation from other task-related cognitive demands[34]. The authors found three small regions that seem to be crucial for time perception: one in the dorsal putamen (bilaterally), another in the left inferior parietal cortex and another at the junction of the AIC and the IFG bilaterally (with no ACC activation). They suggested that the AIC/IFG focus must be “of central importance” in time perception.

Attention. Activation of the AIC (and the ACC) is reported by most studies of goal-directed attention, but these studies often lack comments regarding the role of this activation. One influential model for the neural correlates of the executive control of attention does not include the insula (for example, see REF. 35), and some have argued that attention and consciousness must be different processes[36]. Nevertheless, two recent studies of attention described activation in the AIC/IFG[37,38]. The authors of one study reported decreased activation in the right IFG, ACC and middle frontal gyrus (DLPFC) just before lapses of attention during a monotonous selective-attention task (in which lapses of attention were marked by increased reaction times), and they observed increased activation after such lapses in approximately the same regions (bilateral AIC, ACC, DLPFC, occipital and parietal visual regions), possibly corresponding to renewed attention[37]. They suggested that the AIC/IFG is involved in the stimulus-triggered reorienting of attention and that the ACC is involved in the detection and/or resolution of processing conflicts; however, if the AIC/IFG and the ACC are regarded as complementary limbic sensory and motor regions, respectively (BOX 1), then this response profile would also be consistent with the interpretation that target awareness is engendered in the AIC/IFG and control of directed effort is engendered in the ACC. In another study, a well-practised behavioural task was used to encourage mind-wandering (‘stimulus-independent thought’), and the authors found activation associated with self-reported mind-wandering periods in several regions, particularly the insula (middle and posterior) and the ACC[38]. They interpreted the insular activity with reference to interoception and emotional awareness.

Perceptual decision making. I highlight three seminal reports in this category. First, Ploran *et al.*[39] tracked brain activation in subjects watching a screen on which an image was slowly being revealed. They found a gradual increase in activation in brain regions that are involved in object identification, but a sudden burst of activity in the AIC and the ACC at the moment of recognition (that is, coinciding with the awareness of the percept itself). Second, Thielscher and Pessoa[40] examined a two-choice perceptual task using a graded series of morphed emotional faces (an experimentally generated bi-state percept). They found an inverted-U-shaped correlation between perceptual choice and both reaction time (which represented the decision-making process) and bilateral AIC/IFG (R>L) and ACC activation. They concluded that the AIC “may have been important in the actual generation of the perceptual choice”. Finally, Kikyo *et al.*[41] examined the

Box 3 | **Forebrain asymmetry of emotion**

There are two sides of the brain, and so if there are separate time-based representations of the sentient self that subserve awareness in the anterior insular cortex (AIC) (one in each side), how are they coordinated to generate one unified self? The homeostatic model of awareness presented in this and prior articles[1,78] suggests that there is an energy efficiency-optimal process that is based on the coordinated opponency of the autonomic system — that activity in the right side of the forebrain is associated with energy expenditure, sympathetic activity, arousal, withdrawal (aversive) behaviour and individual-oriented (survival) emotions, and activity in the left side is associated with energy nourishment, parasympathetic activity, relaxation, approach (appetitive) behaviour and group-oriented (affiliative) emotions. This proposal is described in detail in prior articles[78,95]. Briefly, the origin of this asymmetry can be related to the asymmetric autonomic innervation of the heart, and its evolutionary development would have been compelled by the need for energy optimization in the brain (which consumes 25% of the body's energy). This model fits with an accumulating body of psychophysical literature which indicates that the left and right forebrain halves are differentially associated with positive and negative affect[96] and, importantly, with the anatomical and functional asymmetry in the homeostatic afferent input to the insular cortex[5,97,98] and in forebrain cardiac control[99]. It can explain why under particular conditions the AIC is more active on one side (FIG. 2) but also why in most conditions the two sides display joint activity, which mirrors the coordinated sympathetic and parasympathetic control of the heart. The model offers explanations for why positive emotions can reduce or block negative emotions (and vice versa), why the left (affiliative, vagal) side controls deictic pointing and verbal communication, and how increased parasympathetic activity (for example, activation of vagal afferents by gastric distension, slow breathing or elecrical stimulation) can reduce negative emotions (for example, pain). Given the many asymmetries in the activations of the AIC noted in this article, investigations addressing this model in split-brain patients could be enlightening, particularly if performed with those rare patients in whom both the corpus callosum and the anterior commissure are sectioned[100,101].

“feeling of knowing”, which is the subjective sense of knowing a word before recalling it. (The “feeling of knowing” has been interpreted as a subjective feeling that represents the retrievability, accessibility or familiarity of the particular target word, which correlates with the subsequent ease of recall[41,42].) Using a well-tested set of general-knowledge questions without prior exposure or priming, they found pronounced activation in the bilateral AIC/IFG and the ACC that correlated parametrically with the strength of the “feeling of knowing”. The bilateral AIC/IFG was not recruited during the successful recall process itself, which implied to the authors a “particular role in meta-memory processing” for this area.

Cognitive control and performance monitoring. Several reports in this major field of study described strong activation in the AIC. One described functional-connectivity analyses that were performed on brain activation during a combined working-memory and target-switching task; a “cognitive-control network” was identified that includes the bilateral AIC and the ACC[43]. In another report, brain activation was analysed during various cognitive-control tasks and the authors concluded that the bilateral AIC and the ACC form a highly interconnected “core” system for task-dependent control of goal-directed behaviour and sensory processing[44]. A study that used a stop-signal paradigm in which the subjects voluntarily initiated a hand movement but on signalled trials inhibited the movement at the last possible subjective instant found that the bilateral AIC (L>R) and a small region in the MPFC near the ACC region were specifically involved in the active, willed inhibition of a motor act (which the authors called “free won't”, as opposed to free will)[45]. The authors associated the AIC activation with the affective consequence of cancelling a motor intention (frustration), and other investigators in similar studies associated such activation with autonomic arousal[46]. However, an alternative interpretation is that the occurrence of the stop signal naturally elicited an immediately heightened awareness — such heightened awareness would certainly have increased with the rarity of the stop signal, as the investigators found for the AIC[46] and the MPFC region[45]. In another study, performance errors were examined in subjects engaged in a demanding repetitive task, similar to that used in the lapse-of-attention study described above[37], and then independent component analyses and backward deconvolutions were performed to identify brain-activation patterns that preceded errors[47]. The authors found four sets of brain regions in which activity patterns predicted the commission of an error; the first set consisted of the bilateral AIC and the ACC, which they suggested act as a performance monitor. Another set of brain regions they identified consisted of the right AIC/IFG and an MPFC region near the ACC, which they associated with the evaluation of task costs and the maintenance of task effort. In the latter regions, activation declined just before an error occurred and increased after an error had occurred, similar to the pattern of attention-related activity in the study of lapses of attention described above[37]. These results are therefore also consistent with the alternative interpretation that the AIC activity represents awareness and that the ACC activity represents the control of directed effort. A recent study performed several sophisticated connectivity and correlation analyses of attentional transitions and confirmed that the AIC and the ACC act as a cognitive-control network and, further, that the right AIC in particular “plays a critical and causal role in switching between the central executive network and the default-mode” or self-reflective network[48].

Finally, a study by Klein *et al.*[23] may provide direct evidence that the AIC engenders awareness. The authors used an antisaccade task with a distractor (in which subjects were instructed to shift their gaze in the opposite direction to a briefly displayed indicator but were occasionally misdirected by an intervening cue that indicated the other direction), which produced occasional erroneous saccades that the subjects were either aware of (and signalled with a button press) or unaware of. The subjects' error-awareness reports were corroborated by slowed reaction times and improved performance (for most subjects) on trials following ‘aware’ errors but not following ‘unaware’ errors. The fMRI data on error trials revealed activation of the bilateral AIC and three small MPFC regions near the ACC. By contrasting brain activity during aware errors with that during unaware errors, the authors found activation only in the left inferior AIC (similar activation in the right AIC was just subthreshold). Significantly, activation near the ACC was not associated with error awareness. The authors suggested that the activity of the AIC during aware errors might be explained by interoceptive awareness of greater autonomic responses to aware errors (which have been documented previously), but they also recognized that the AIC activity and error awareness might precede the autonomic response[23]. They recommended the use of electroencephalographic recordings to resolve this uncertainty, because the temporal resolution of fMRI is too low.

Box 4 | **Alternative perspectives**

There are many alternative views of the neural substrates that are involved in human awareness or consciousness. Two particular viewpoints suggest that the anterior cingulate cortex (ACC) has a singular role in the representation of the self and emotional awareness of internal processes[102,103], but neither has incorporated the anatomical perspective that the anterior insular cortex (AIC) and the ACC are complementary limbic regions or the evidence reviewed here.

Some investigators suggest that the posteromedial cortex (including the cingulate and the precuneus) provides the basis for self-awareness (for example, see REF. 104). However, this area is part of the so-called default network, which seems to be involved in self-reflective episodic memory retrieval, and activity in this area is inversely correlated in functional-imaging studies with the activation in the AIC that is associated with awareness and task-related attention[44,90]. The default network also seems to be present in the macaque monkey[105].

There are numerous proposals for the neural basis of the various forms of the clinical syndrome anosognosia (a lack of awareness of a functional impairment), but these are complicated by the multiple levels of integration that are required for each perceptual capacity and by confounding issues in the clinical documentation[67,106]. Recent clinical and anatomical correlations in patients with anosognosia for hemiplegia and hemianaesthesia have focused on the insula[66,67]. Prior studies implicated the right inferior parietal cortex and the angular gyrus, but recent authors agree with the idea that this region processes a representation of extrapersonal space that incorporates self-generated movements, and that this module precedes the integration of information about the self in the AIC[66,67,106], although this idea remains to be tested.

Several authors suggest the existence of different levels of awareness or consciousness[51,70,107]. Although this view is not incompatible with the present hypothesis, because more than one conceptual level of awareness might be instantiated in the AIC (including a comparator that could feel like an 'observer'), other investigators might regard it as unlikely, because they prefer the notion that consciousness depends on recurrent activity in a distributed network across the entire brain (for example, see REF. 77). For example, one author suggested that the orbitofrontal cortex is part of a global workspace that underlies consciousness[108], although its role in hedonic valuation (especially for feeding behaviour) is well-developed in all mammals and it is not disproportionately enlarged in humans[109]. Nevertheless, the AIC certainly does not operate autonomously and the evidence reviewed here indicates that it is involved in more than one functional network; further, there are probably numerous modules in the AIC, the complexity of which might increase from the posterior to the anterior, that could accommodate higher levels of abstraction[21,22,83,110]. For example, although the hurt that is associated with social exclusion was reported to overlap with the AIC region that is activated during physical pain, a close examination of the imaging data reveals that in fact the activation lies considerably more anterior[111].

The role of the AIC

This brief review reveals that an astonishing number of recent studies from a broad range of fields reported activation of the AIC. These studies associate the AIC not just with all subjective feelings but also with attention, cognitive choices and intentions, music, time perception and, unmistakably, awareness of sensations and movements[2,3,11–14], of visual and auditory percepts[27–29,31,32], of the visual image of the self[15], of the reliability of sensory images[30] and subjective expectations[24,25], and of the trustworthiness of other individuals (see REF. 1 for further detail). In several key experiments, the AIC was activated without apparent activation in the ACC[11–14,16,23–25,34]. No other region of the brain is activated in all of these tasks, and the only feature that is common to all of these tasks is that they engage the awareness of the subjects. Thus, in my opinion, the accumulated evidence compels the hypothesis that the AIC engenders human awareness.

What is awareness? Until we know more about how brains work, only a working definition is possible. I regard awareness as knowing that one exists (the feeling that 'I am'); an organism must be able to experience its own existence as a sentient being before it can experience the existence and salience of anything else in the environment. One proposal holds that awareness of any object requires, first, a mental representation of oneself as a feeling (sentient) entity; second, a mental representation of that object; and third, a mental representation of the salient interrelationship between oneself and that object in the immediate moment ('now')[49,50]. As in Damasio's "neural self" (REF. 51), this formulation inherently creates a subjective ('personal') perspective that differentiates inner and outer realms, because the inner feelings that underlie one's representation of oneself as a sentient being are accessible only from one's own brain[51,52]. In this view, one can lose the ability to perceive a portion of extrapersonal space (for example, following damage to right parietal cortex), an impairment in the movement of one's limbs (anosognosia for hemiplegia following damage to the mid-insula) or one's entire autobiographical history and yet maintain phenomenal awareness of feelings and existence (for example, the patient with only visceral feelings remaining and an intact anterior insula[51], or patient R.B., who lives in a moving 40-second window of present time[51,52]). A further proposal is that a reflective awareness of oneself across time that can compare the effects of one's actions now, in the past and in the future was required for the evolution of deliberate social signalling (intentional emotional interaction between individuals)[49,53]. Some investigators view this capacity as a higher-order level of awareness that might provide the introspective feeling of subjectivity[51,53] (see BOX 4 and further discussion below). The mirror test for self-recognition has been used as an operational test for self-awareness, and although objections to this test have been raised, I concur with the view that it has validity as a sufficient but not necessary criterion[54–57]; that is, a feeling of ownership of and identification with movements and emotional gestures reflected in a mirror is possible only with a mental representation of a sentient self. Recently, it has also been proposed that awareness in humans could be measured with post-decision wagering[58].

The implications of the imaging data. The results highlighted in the categories 'Interoception', 'Awareness of body movement' and 'Emotional awareness' indicate that the AIC provides a unique neural substrate that instantiates all subjective feelings from the body and feelings of emotion in the immediate present (now). The anatomical posterior-to-mid-to-anterior progression of integration from the primary interoceptive representations to the middle integration zone to the ultimate representation of all of one's feelings (that is, the sentient self) is now well documented and supports the proposition that subjective awareness is built on homeostasis[1,4,51,61]. The noted studies on the perception of bistable percepts[27–29], time synchronization[30], inspection time[31], the attentional blink[32] and perceptual decision making[39,40] all imply directly that the AIC supports awareness of the immediate moment with a coherent representation of 'my feelings' about 'that thing'. The demonstration that the AIC activates during self-recognition satisfies the criterion of instantiation of self-awareness, equivalent to the mirror test[15], because it reveals a subjective feeling of enhanced emotional salience in the representation of the sentient self during self-identification. Further, the demonstration that AIC activation is correlated with the "feeling of knowing" (REF. 41) suggests that the AIC also engenders awareness of feelings that are associated with mental constructs and operations[59,60].

The highlighted findings in the categories 'Risk, uncertainty and anticipation', 'Time perception' and 'Cognitive control and performance monitoring' are consistent with the notion that the AIC contains a representation of the sentient self not only in the immediate moment but at each moment across a finite period of time. The AIC is a central component of a neural substrate that represents the passage of time[34], it is sensitive to time synchronization[30] and it is uniquely involved in automatic comparisons of feelings in the present moment with those in the past and the future[25]. These findings also indicate that the AIC incorporates a 'buffer', or comparator, that is used for such comparisons. These observations suggest that the AIC fulfils a requirement of the proposed[49,53] evaluative and predictive role of awareness in the evolution of emotional communication, and that it affords an integral mechanism for decision making. (Interestingly, a stable comparator might be perceived introspectively as an ephemeral observer, or a Cartesian theater, that nonetheless cannot 'see' itself, as described[61] for 'consciousness'.) Significantly, the evidence that the AIC is also associated with predictions of future feelings can explain its involvement in the distorted interoceptive predictions that are associated with anxiety and functional somatic disorders[62,63].

The findings I highlighted on perceptual decision making ("choice")[40] and cognitive control ("free won't" (REF. 45), preparation for error commission[47] and attentional transitions[48]) imply that the AIC has a role in the subjective guidance of mental and physical behaviour. This inference is consistent with the introspective feeling that 'I' am not simply a passive observer (whether this is an illusion or not; see REF. 64). Such involvement does not contradict the idea that the ACC subserves volitional agency (BOX 1), an idea that is supported by the ACC's joint (with the AIC) activation in almost all of these studies and by its association with action and the descending limbic motor system[1,65].

Finally, the highlighted findings on the activation of the AIC during musical enjoyment and 'heightened awareness' point to specific characteristics of the AIC that need to be explained by any model of its role in awareness.

Clinical observations. Clinical observations offer corroborative evidence for the hypothesis that the AIC engenders human awareness. Supplementary information S1 (table) lists clinical reports that indicate involvement of the AIC and the mid-insula with conditions that include anosognosia, anergia, anxiety, alexithymia, depression, aphasia, amusia, ageusia, drug craving, eating disorders, conduct disorder, panic disorder, mood disorders, post-traumatic stress disorder, schizophrenia, Smith–Magenis syndrome, cardiac arrhythmia, vertigo and frontotemporal dementia (FTD). Many of these reports are quite narrowly focused and do not describe comprehensive behavioural testing, whereas the evidence reviewed above suggests that most patients with insular damage could have several significant neurological deficits.

Several clinical studies indicate that damage to or abnormal activation or development of the AIC is associated with altered awareness. Two studies reported that anosognosia for hemiplegia is specifically associated with damage in the right mid-insula[66,67]; adolescents with conduct disorder were found to have a significant decrease in grey matter volume in the bilateral AIC that correlated with a lack of empathy and with aggressive behaviour[68]; patients with borderline personality disorder who are incapable of cooperating do not display the graded activation of the AIC that is associated with awareness of social gestures in normal subjects[69]; high-functioning people with autism displayed increased alexithymia and decreased empathy, both of which were correlated with reduced activation in the AIC (in a task in which the subjects assessed their feelings about unpleasant images)[70] (however, see REFS 71,72); hyperactivity in the right AIC was selectively associated with anxiety[62]; infarcts of the AIC were reported to produce anergia, or complete listlessness[73]; and congenital malformation of the bilateral insula (Smith–Magenis syndrome) produces childhood mental retardation and the disruption of self-guided behaviour[74]. Most significantly, patients with FTD associated with degenerate fronto-insular and cingulate cortices display a selective loss of self-conscious behaviours and a loss of emotional awareness of self and others[75]; in fact, Seeley *et al.* reported the landmark finding that the loss of subjective emotional awareness in patients with FTD is specifically associated with the degeneration of VENs[76]. These reports are especially notable in light of the obvious difficulties in demonstrating deficits in emotional awareness in adult humans who have well-established behavioural patterns.

Summary. Thus, the available data provide compelling support for the concept that the AIC contains the anatomical substrate for the evolved capacity of humans to be aware of themselves, others and the environment. In my opinion, these data suggest that the AIC uniquely fulfils the requirements to be the neural correlate of awareness. The brain is well organized into networks that distribute functionality across multiple sites, and the localization of awareness of feelings and existence in a single substrate might seem unlikely[67,77]. Nevertheless, the evidence suggests that the AIC and the adjoining frontal operculum (on both the left and right sides) contains an ultimate representation of the sentient self in humans (and perhaps hominoid primates, elephants and whales; BOX 2). These data recommend a discussion of the possibility that the AIC is a "neural correlate of consciousness" (REF. 77) and of the question of how the AIC might engender awareness.

A model for awareness in the AIC

In a recently published book chapter[78], I expanded on the ideas presented in the 2002 Perspective article[1] by outlining a theoretical model for the structural instantiation of awareness in the AIC. The evidence described above of a role for the AIC in awareness is consistent with this model, and thus I elaborate the model here and incorporate these recent findings.

Briefly, in this model the cortical basis for awareness is an ordered set of representations of all feelings at each immediate moment extending across a finite period of time. The key to the cortical (that is, mental) representation of the sentient self is the integration of salience across all relevant conditions at each moment. The salience of any factor is determined by its significance for the maintenance and advancement of the individual and the species. At the most fundamental level, this means the energy-efficient maintenance of the health of the physical body (and the brain) — in other words, homeostasis. In this view, the neural basis for awareness is the neural representation of the physiological condition of the body, and the homeostatic neural construct for a feeling from the body is the foundation for the encoding of all feelings[1,78].

The phylogenetically new homeostatic afferent pathway from lamina I and the solitary nucleus in primates provides the basis for the sense of the physiological condition of the entire body in the posterior insular cortex[1]; this includes numerous individually mapped and distinct feelings from the body. These neural constructs are then re-represented in the mid-insula and again in the AIC (on the left or right side or both, depending on the source of the activity; BOX 3). The mid-insula integrates these homeostatic re-representations with activity that is associated with emotionally salient environmental stimuli of many sensory modalities, probably by way of input from higher-order sensory regions, the temporal pole and the amygdala. Recent functional connectivity analyses indicate that the mid-insula is also modulated directly by the ventral striatum (the nucleus accumbens)[79], which provides an important incentive, or hedonic, signal for the integration of salience. Thus, this posterior-to-anterior progression — which is consistent with the general processing gradient for increasing complexity in the frontal cortex[22,65] and with the enormous expansion of the anterior insula across hominoid primates — provides a substrate for the sequential integration of homeostatic conditions with the sensory environment and with motivational, hedonic and social conditions represented in other parts of the brain, and this substrate is constructed on the foundation provided by the feelings from the body (FIG. 3a).

I propose that the integration of salience across all of these factors culminates in a unified final meta-representation of the 'global emotional moment' near the junction of the anterior insula and the frontal operculum. This processing stage is key, because it generates an image of 'the material me' (or the sentient self) at one moment in time — 'now'. An anatomical repetition of this fundamental unit, indexed by an endogenous timebase, is all that is required to generate a set of repeated meta-representations of global emotional moments that extends across a finite period of time, and this anatomical structure (a 'meta-memory') provides the basis for the continuity of subjective emotional awareness in a finite present[78] (FIG. 3b). The recent data emphasize that storage buffers for individual global emotional moments must be present to enable comparisons of past, present and future feelings; this would instantiate a reflexive 'observer', as noted above. The anticipatory global emotional moments must be influenced by stored representations of expectations that are based on acquired internal models of one's own and others' behaviour. A straightforward, although speculative, anatomical inference of this model is that meta-representations of global emotional moments might be engendered by clusters of VENs in the AIC, and that these are interconnected with similar clusters of VENs in the ACC and probably in the AIC and ACC on the opposite side (BOX 1), but the connections and functions of VENs still need to be identified. I believe that each successive stage of integration in this model could have provided an evolutionary advantage, in that it would improve emotional communication between conspecifics — crucial for hominoid primates[80]

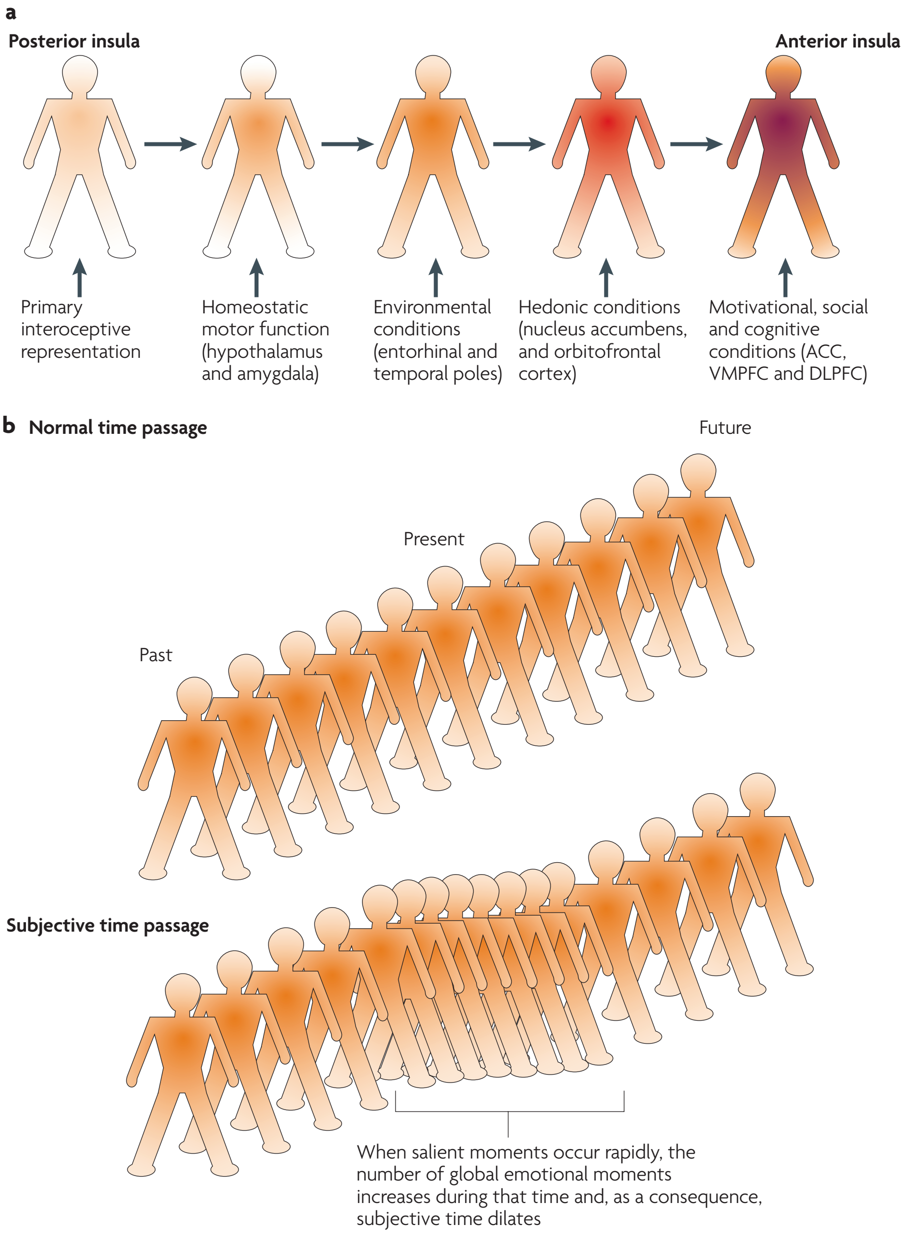


Figure 3 | **A proposed model of awareness.** Cartoons illustrating features of the proposed structural model of awareness. **a** | The posited integration of salient activity, progressing from the posterior insula (left) to the anterior insula (right). The primary interoceptive representations of feelings from the body provide a somatotopic foundation that is anchored by the associated homeostatic effects on cardiorespiratory function, as indicated by the focus of the colours in the chest. The integration successively includes homeostatic, environmental, hedonic, motivational, social and cognitive activity to produce a 'global emotional moment', which represents the sentient self at one moment of time. **b** | The top cartoon shows how a series of global emotional moments can produce a cinemascopic 'image' of the sentient self across time. The lower cartoon shows how the proposed model can produce a subjective dilation of time during a period of high emotional salience, when global emotional moments are rapidly 'filled up'. ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex.

— and that each stage would have been easily realizable by evolutionary neuroanatomical modifications.

Implications and future directions

It is fascinating that the proposed model for awareness in the AIC produces an emergent basis for the uniquely human faculty of music: viewed as the rhythmic temporal progression of emotionally laden moments, music arises as a natural concomitant of this structural model. The engagement of the AIC by emotional feelings, by the feeling of movement and by the sense of time encourages the view that this model can explain the observed activation of the AIC by rhythm[16] and by musical enjoyment[17], as well as the primal emotional effects of communal music-making, because music would inherently involve the core of awareness.

This model also suggests a mechanism for the subjective time dilation, or slowing of time, that occurs during an intensely emotional period[81]. A high rate of salience accumulation would 'fill up' global emotional moments quickly, because the information capacity of the neural instantiation of a global emotional moment must be finite. Thus, the endogenous timebase would effectively speed up during such a period (FIG. 3b) and, consequently, time would appear to stand still to the 'observer'. Psychophysical data from rapid-visual-search studies suggest that the maximal rate of passage of individual moments is ~8 Hz[31]. A similar process for the recruitment of global emotional moments could provide the basis for 'heightened awareness' of the immediate moment and for the enhanced activation of the AIC that is associated with such moments.

In this model, the close integration between the AIC and the ACC implies that activity in the AIC can incorporate the urges of the volitional agent that is represented in the ACC, and also that feelings in the AIC can be modulated by that agent[82], so that each global emotional moment comprises both feelings and motivations (BOX 1). Indeed, the representation in the sentient self of the active behavioural agent (the 'I') fills a gap in the 'somatic marker' hypothesis[51] and challenges a main criticism of the James–Lange theory[51], namely that the theory did not allow for feelings of internally generated emotion. In the model presented in this article, all stimuli, incentives, intentions and cognitions that have salience are represented by feelings, a crucial neuropsychological construct composed of nested sets of integrative associations that are elaborated on an interoceptive template and endowed with characteristic homeostatic sequelae (and thus, all feelings 'move the heart'). In this model, feelings are the computational common currency of awareness[59,60].

Finally, this model includes the possibility that emotional behaviours can occur without awareness (that is, by activation of the ACC without integration in the AIC), it implies that animals without these structures are not aware in the same way that we are (BOX 2) and it provides a ready basis for the inclusion of a module that would assign responsibility for the behavioural agent's actions to the sentient self[64].

It is important to note this model's current limitations. It does not explain how a feeling is constructed, the nature of the timebase and its relation to homeostatic activity (such as one's heartbeat), the mechanism for shifting moments across time, the neural metric of salience, the differentiation of emotions, the necessary dynamic connectivity of global emotional moments[83] or the integration between the two sides of the AIC (BOX 3). It does not specify the location of memories of past feelings or the location of the internal behavioural models that produce anticipatory feelings. The evidence reviewed above suggests that the final representation of the sentient self in the AIC may consist of one coherent somatotopic map that has sufficiently global characteristics and dynamic connectivity to encompass all possible feelings, but few studies have compared different emotions and different body-part associations. It is even difficult to systematically predict how lesions of the AIC and the ACC should differ in terms of their effects considering their intimate connectivity (for example, see the contrasting results in the literature on alexithymia[70–72]). I look forward particularly to the future identification of the various functional modules in the AIC and the characteristics and the 'language' of VENs. There are many other questions that need to be addressed, some of which are listed in BOX 5.

A. D. (Bud) Craig is at the Atkinson Research Laboratory, Barrow Neurological Institute, Phoenix, Arizona 85013, USA.

e-mail: bcraig@chw.edu

doi:10.1038/nrn2555

Box 5 | **Future research questions following from the model**

What are the anatomical connections of the anterior insular cortex (AIC)? Modern imaging studies using diffusion spectrum imaging and functional and effective connectivity analyses are needed that incorporate the AIC's dynamic connectivity[83]. Comprehensive analysis of the hodology of the macaque insular cortex using classic tract-tracing methods is also needed.

How do the two sides of the AIC differ, and how do they interact? Does one side lead[48] and the other side monitor[23,48] at different times? Direct statistical comparisons of laterality in activation are needed. Advanced analyses based on demonstrated asymmetries (FIG. 2) can be designed; for example, one could examine changes in activation patterns and effective connectivity during the modulation of pain by pleasant music[112].

Is there one somatotopic map that provides a common-resource pool of 'global emotional moments', represents all feelings and is dynamically accessed at each moment? Or are there numerous modules in the AIC that are coordinated to represent different feelings at each global emotional moment? For example, evidence suggests that the eyes and the face are represented in the anterior ventral AIC and that the hand and the foot are represented more posteriorly, which is consistent with the presence of one map; however, the somatotopy in the one study that included stimulation of multiple body parts is reversed[10].

Similarly, is there only one module in each AIC that represents time, as suggested by the tiny areas of activation in the AIC found in one study[34]? And does the activity in these areas correlate with subjective time dilation? Are these areas asymmetric on the two sides with respect to the contrasting effects of arousal and pleasant mood on time perception[113]?

How are comparisons made between feelings at different points in time? Where are the intermediate 'meta-memory' buffers and how are they interconnected?

The neuropsychological construct called a 'feeling' is crucial. Why is it important that this construct has a homeostatic basis? What do feelings from the body and feelings about objects or people or cognitions have in common? Do all feelings have autonomic sequelae — that is, do they 'move the heart'? Can every thought be regarded as a feeling? Are feelings indeed the common currency of awareness?

Does emotional congruence between individuals reflect homeostatic resonance?

Do elephants really make infrasonic music together? What about whales?

Infants do not pass the mirror test or show self-conscious behaviours until they are ~18 months old[50,53]. Does the connectivity of their AIC and anterior cingulate cortex (ACC) show a similar developmental threshold?

The activation of the AIC or the ACC has been used for biofeedback training. Could this application be refined in light of the considerations set out in this article?

1. Craig, A. D. How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Rev. Neurosci.* **3**, 655–666 (2002).
2. Craig, A. D., Chen, K., Bandy, D. & Reiman, E. M. Thermosensory activation of insular cortex. *Nature Neurosci.* **3**, 184–190 (2000).
3. Critchley, H. D., Wiens, S., Rotshtein, P., Ohman, A. & Dolan, R. J. Neural systems supporting interoceptive awareness. *Nature Neurosci.* **7**, 189–195 (2004).
4. Barrett, L. F., Quigley, K. S., Bliss-Moreau, E. & Aronson, K. R. Interoceptive sensitivity and self-reports of emotional experience. *J. Pers. Soc. Psychol.* **87**, 684–697 (2004).
5. Stephan, E. *et al.* Functional neuroimaging of gastric distention. *J. Gastrointest. Surg.* **7**, 740–749 (2003).
6. Phillips, M. L. *et al.* The effect of negative emotional context on neural and behavioural responses to oesophageal stimulation. *Brain* **126**, 669–684 (2003).
7. 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).
8. Kong, J. *et al.* Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity. *Hum. Brain Mapp.* **27**, 715–721 (2006).
9. Singer, T. *et al.* Empathy for pain involves the affective but not sensory components of pain. *Science* **303**, 1157–1162 (2004).
10. 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).
11. Farrer, C. & Frith, C. D. Experiencing oneself vs another person as being the cause of an action: the neural correlates of the experience of agency. *Neuroimage* **15**, 596–603 (2002).
12. Farrer, C. *et al.* Modulating the experience of agency: a positron emission tomography study. *Neuroimage* **18**, 324–333 (2003).
13. Tsakiris, M., Hesse, M. D., Boy, C., Haggard, P. & Fink, G. R. Neural signatures of body ownership: a sensory network for bodily self-consciousness. *Cereb. Cortex* **17**, 2235–2244 (2007).
14. Mutschler, I. *et al.* A rapid sound-action association effect in human insular cortex. *PLoS ONE* **2**, e259 (2007).
15. Devue, C. *et al.* Here I am: the cortical correlates of visual self-recognition. *Brain Res.* **1143**, 169–182 (2007).
16. Platel, H. *et al.* The structural components of music perception. A functional anatomical study. *Brain* **120**, 229–243 (1997).
17. Koelsch, S., Fritz, T., v. Cramon, D. Y., Muller, K. & Friederici, A. D. Investigating emotion with music: an fMRI study. *Hum. Brain Mapp.* **27**, 239–250 (2006).
18. Ackermann, H. & Riecker, A. The contribution of the insula to motor aspects of speech production: a review and a hypothesis. *Brain Lang.* **89**, 320–328 (2004).
19. Seeley, W. W. *et al.* Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci.* **27**, 2349–2356 (2007).
20. Hennenlotter, A. *et al.* A common neural basis for receptive and expressive communication of pleasant facial affect. *Neuroimage* **26**, 581–591 (2005).
21. Jabbi, M., Swart, M. & Keysers, C. Empathy for positive and negative emotions in the gustatory cortex. *Neuroimage* **34**, 1744–1753 (2007).
22. Koechlin, E. & Jubault, T. Broca's area and the hierarchical organization of human behavior. *Neuron* **50**, 963–974 (2006).
23. Klein, T. A. *et al.* Neural correlates of error awareness. *Neuroimage* **34**, 1774–1781 (2007).
24. Seymour, B. *et al.* Temporal difference models describe higher-order learning in humans. *Nature* **429**, 664–667 (2004).
25. Preuschoff, K., Quartz, S. R. & Bossaerts, P. Human insula activation reflects risk prediction errors as well as risk. *J. Neurosci.* **28**, 2745–2752 (2008).
26. Knutson, B., Rick, S., Wimmer, G. E., Prelec, D. & Loewenstein, G. Neural predictors of purchases. *Neuron* **53**, 147–156 (2007).
27. Kondo, H. M. & Kashino, M. Neural mechanisms of auditory awareness underlying verbal transformations. *Neuroimage* **36**, 123–130 (2007).
28. Pressnitzer, D. & Hupe, J. M. Temporal dynamics of auditory and visual bistability reveal common principles of perceptual organization. *Curr. Biol.* **16**, 1351–1357 (2006).
29. Sterzer, P. & Kleinschmidt, A. A neural basis for inference in perceptual ambiguity. *Proc. Natl Acad. Sci. USA* **104**, 323–328 (2007).
30. Bushara, K. O., Grafman, J. & Hallett, M. Neural correlates of auditory-visual stimulus onset asynchrony detection. *J. Neurosci.* **21**, 300–304 (2001).
31. Deary, I. J. *et al.* The functional anatomy of inspection time: an event-related fMRI study. *Neuroimage* **22**, 1466–1479 (2004).
32. Kranczioch, C., Debener, S., Schwarzbach, J., Goebel, R. & Engel, A. K. Neural correlates of conscious perception in the attentional blink. *Neuroimage* **24**, 704–714 (2005).
33. Coull, J. T. fMRI studies of temporal attention: allocating attention within, or towards, time. *Brain Res. Cogn. Brain Res.* **21**, 216–226 (2004).
34. Livesey, A. C., Wall, M. B. & Smith, A. T. Time perception: manipulation of task difficulty dissociates clock functions from other cognitive demands. *Neuropsychologia* **45**, 321–331 (2007).
35. Fan, J. *et al.* The relation of brain oscillations to attentional networks. *J. Neurosci.* **27**, 6197–6206 (2007).
36. Koch, C. & Tsuchiya, N. Attention and consciousness: two distinct brain processes. *Trends Cogn Sci.* **11**, 16–22 (2007).
37. Weissman, D. H., Roberts, K. C., Visscher, K. M. & Woldorff, M. G. The neural bases of momentary lapses in attention. *Nature Neurosci.* **9**, 971–978 (2006).
38. Mason, M. F. *et al.* Wandering minds: the default network and stimulus-independent thought. *Science* **315**, 393–395 (2007).
39. Ploran, E. J. *et al.* Evidence accumulation and the moment of recognition: dissociating perceptual recognition processes using fMRI. *J. Neurosci.* **27**, 11912–11924 (2007).
40. Thielscher, A. & Pessoa, L. Neural correlates of perceptual choice and decision making during fear-disgust discrimination. *J. Neurosci.* **27**, 2908–2917 (2007).
41. Kikyo, H., Ohki, K. & Miyashita, Y. Neural correlates for feeling-of-knowing: an fMRI parametric analysis. *Neuron* **36**, 177–186 (2002).
42. Yonelinas, A. P., Otten, L. J., Shaw, K. N. & Rugg, M. D. Separating the brain regions involved in recollection and familiarity in recognition memory. *J. Neurosci.* **25**, 3002–3008 (2005).
43. Cole, M. W. & Schneider, W. The cognitive control network: integrated cortical regions with dissociable functions. *Neuroimage* **37**, 343–360 (2007).
44. Dosenbach, N. U. *et al.* Distinct brain networks for adaptive and stable task control in humans. *Proc. Natl Acad. Sci. USA* **104**, 11073–11078 (2007).
45. Brass, M. & Haggard, P. To do or not to do: the neural signature of self-control. *J. Neurosci.* **27**, 9141–9145 (2007).
46. Ramautar, J. R., Slagter, H. A., Kok, A. & Ridderinkhof, K. R. Probability effects in the stop-signal paradigm: the insula and the significance of failed inhibition. *Brain Res.* **1105**, 143–154 (2006).
47. Eichele, T. *et al.* Prediction of human errors by maladaptive changes in event-related brain networks. *Proc. Natl Acad. Sci. USA* **105**, 6173–6178 (2008).
48. Sridharan, D., Levitin, D. J. & Menon, V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc. Natl Acad. Sci. USA* **105**, 12569–12574 (2008).
49. Frith, C., Perry, R. & Lumer, E. The neural correlates of conscious experience: an experimental framework. *Trends Cogn. Sci.* **3**, 105–114 (1999).
50. Lewis, M. in *Handbook of Emotions* 3rd edn (eds Lewis, M., Haviland-Jones, J. M. & Barrett, L. F.) 304–319 (Guilford, New York, 2008).
51. Damasio, A. R. *Descartes' Error: Emotion, Reason, and the Human Brain* (Putnam, New York, 1993).
52. Churchland, P. S. Self-representation in nervous systems. *Science* **296**, 308–310 (2002).
53. Frith, C. D. & Frith, U. Social cognition in humans. *Curr. Biol.* **17**, R724–R732 (2007).
54. Macphail, E. M. *The Evolution of Consciousness* (Oxford Univ. Press, Oxford, 1998).
55. de Waal, F. B. The thief in the mirror. *PLoS Biol.* **6**, e201 (2008).
56. Reiss, D. & Marino, L. Mirror self-recognition in the bottlenose dolphin: a case of cognitive convergence. *Proc. Natl Acad. Sci. USA* **98**, 5937–5942 (2001).
57. Prior, H., Schwarz, A. & Gunturkun, O. Mirror-induced behavior in the magpie (*Pica pica*): evidence of self-recognition. *PLoS Biol.* **6**, e202 (2008).
58. Persaud, N., McLeod, P. & Cowey, A. Post-decision wagering objectively measures awareness. *Nature Neurosci.* **10**, 257–261 (2007).
59. Ruys, K. I. & Stapel, D. A. The secret life of emotions. *Psychol. Sci.* **19**, 385–391 (2008).
60. Duncan, S. & Barrett, L. F. Affect is a form of cognition: a neurobiological analysis. *Cogn. Emot.* **21**, 1184–1211 (2007).
61. James, W. The Principles of Psychology. *Classics in the History of Psychology* [online], http://psychclassics.yorku.ca/James/Principles/ (1890).
62. Paulus, M. P. & Stein, M. B. An insular view of anxiety. *Biol. Psychiatry* **60**, 383–387 (2006).
63. Mayer, E. A., Naliboff, B. D. & Craig, A. D. Neuroimaging of the brain-gut axis: from basic understanding to treatment of functional GI disorders. *Gastroenterology* **131**, 1925–1942 (2006).
64. Wegner, D. M. *The Illusion of Conscious Will* (MIT Press, Cambridge, Massachusetts, 2008).
65. Amodio, D. M. & Frith, C. D. Meeting of minds: the medial frontal cortex and social cognition. *Nature Rev. Neurosci.* **7**, 268–277 (2006).
66. Karnath, H. O., Baier, B. & Nagele, T. Awareness of the functioning of one's own limbs mediated by the insular cortex? *J. Neurosci.* **25**, 7134–7138 (2005).
67. Spinazzola, L., Pia, L., Folegatti, A., Marchetti, C. & Berti, A. Modular structure of awareness for sensorimotor disorders: evidence from anosognosia for hemiplegia and anosognosia for hemianaesthesia. *Neuropsychologia* **46**, 915–926 (2008).
68. Sterzer, P., Stadler, C., Poustka, F. & Kleinschmidt, A. A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. *Neuroimage* **37**, 335–342 (2007).
69. King-Casas, B. *et al.* The rupture and repair of cooperation in borderline personality disorder. *Science* **321**, 806–810 (2008).
70. Silani, G. *et al.* Levels of emotional awareness and autism: an fMRI study. *Soc. Neurosci.* **3**, 97–112 (2008).
71. Moriguchi, Y. *et al.* Empathy and judging other's pain: an fMRI study of alexithymia. *Cereb. Cortex* **17**, 2223–2234 (2007).
72. Kano, M. *et al.* Specific brain processing of facial expressions in people with alexithymia: an $H_2^{15}O$-PET study. *Brain* **126**, 1474–1484 (2003).
73. Manes, F., Paradiso, S. & Robinson, R. G. Neuropsychiatric effects of insular stroke. *J. Nerv. Ment. Dis.* **187**, 707–712 (1999).
74. Boddaert, N. *et al.* Anatomical and functional brain imaging evidence of lenticulo-insular anomalies in Smith Magenis syndrome. *Neuroimage* **21**, 1021–1025 (2004).
75. Sturm, V. E., Rosen, H. J., Allison, S., Miller, B. L. & Levenson, R. W. Self-conscious emotion deficits in frontotemporal lobar degeneration. *Brain* **129**, 2508–2516 (2006).
76. Seeley, W. W. *et al.* Early frontotemporal dementia targets neurons unique to apes and humans. *Ann. Neurol.* **60**, 660–667 (2006).
77. Christensen, M. S., Ramsoy, T. Z., Lund, T. E., Madsen, K. H. & Rowe, J. B. An fMRI study of the neural correlates of graded visual perception. *Neuroimage* **31**, 1711–1725 (2006).
78. Craig, A. D. in *Handbook of Emotions* 3rd edn (eds Lewis, M., Haviland-Jones, J. M. & Barrett, L. F.) 272–288 (Guilford, New York, 2008).
79. Menon, V. & Levitin, D. J. The rewards of music listening: response and physiological connectivity of the mesolimbic system. *Neuroimage* **28**, 175–184 (2005).
80. Dunbar, R. I. & Shultz, S. Evolution in the social brain. *Science* **317**, 1344–1347 (2007).
81. Tse, P. U., Intriligator, J., Rivest, J. & Cavanagh, P. Attention and the subjective expansion of time. *Percept. Psychophys.* **66**, 1171–1189 (2004).
82. Sarinopoulos, I., Dixon, G. E., Short, S. J., Davidson, R. J. & Nitschke, J. B. Brain mechanisms of expectation associated with insula and amygdala response to aversive taste: implications for placebo. *Brain Behav. Immun.* **20**, 120–132 (2006).
83. Jabbi, M., Bastiaansen, J. & Keysers, C. A common anterior insula representation of disgust observation, experience and imagination shows divergent functional connectivity pathways. *PLoS ONE* **3**, e2939 (2008).
84. Penfield, W. & Faulk, M. E. The insula. *Brain* **78**, 30–470 (1955).
85. Mesulam, M.-M. & Mufson, E. J. Insula of the old world monkey. III: Efferent cortical output and comments on function. *J. Comp. Neurol.* **212**, 38–52 (1982).
86. Saper, C. B. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu. Rev. Neurosci.* **25**, 433–469 (2002).

87. Heimer, L. & Van Hoesen, G. W. The limbic lobe and its output channels: implications for emotional functions and adaptive behavior. *Neurosci. Biobehav. Rev.* **30**, 126–147 (2006).
88. Nimchinsky, E. A. *et al.* A neuronal morphologic type unique to humans and great apes. *Proc. Natl Acad. Sci. USA* **96**, 5268–5273 (1999).
89. Allman, J. M., Watson, K. K., Tetreault, N. A. & Hakeem, A. Y. Intuition and autism: a possible role for Von Economo neurons. *Trends Cogn. Sci.* **9**, 367–373 (2005).
90. Seeley, W. W. *et al.* Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci.* **27**, 2349–2356 (2007).
91. Seeley, W. W. *et al.* Divergent social functioning in behavioral variant frontotemporal dementia and Alzheimer disease: reciprocal networks and neuronal evolution. *Alzheimer Dis. Assoc. Disord.* **21**, S50–S57 (2007).
92. Hakeem, A. Y. *et al.* Von Economo neurons in the elephant brain. *Anat. Rec.* (in the press).
93. Hof, P. R. & Van der Gucht, E. Structure of the cerebral cortex of the humpback whale, *Megaptera novaeangliae* (Cetacea, Mysticeti, Balaenopteridae). *Anat. Rec. (Hoboken)* **290**, 1–31 (2007).
94. Plotnik, J. M., de Waal, F. B. & Reiss, D. Self-recognition in an Asian elephant. *Proc. Natl Acad. Sci. USA* **103**, 17053–17057 (2006).
95. Craig, A. D. Forebrain emotional asymmetry: a neuroanatomical basis? *Trends Cogn. Sci.* **9**, 566–571 (2005).
96. Davidson, R. J. Well-being and affective style: neural substrates and biobehavioural correlates. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **359**, 1395–1411 (2004).
97. Rosenkranz, M. A. *et al.* Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. *Proc. Natl Acad. Sci. USA* **102**, 13319–13324 (2005).
98. Henderson, L. A. *et al.* Neural responses during Valsalva maneuvers in obstructive sleep apnea syndrome. *J. Appl. Physiol.* **94**, 1063–1074 (2003).
99. Oppenheimer, S. M., Gelb, A., Girvin, J. P. & Hachinski, V. C. Cardiovascular effects of human insular cortex stimulation. *Neurology* **42**, 1727–1732 (1992).
100. Gazzaniga, M. S. Forty-five years of split-brain research and still going strong. *Nature Rev. Neurosci.* **6**, 653–659 (2005).
101. Uddin, L. Q., Rayman, J. & Zaidel, E. Split-brain reveals separate but equal self-recognition in the two cerebral hemispheres. *Conscious. Cogn.* **14**, 633–640 (2005).
102. Lane, R. D. Neural substrates of implicit and explicit emotional processes: a unifying framework for psychosomatic medicine. *Psychosom. Med.* **70**, 214–231 (2008).
103. Lieberman, M. D. Social cognitive neuroscience: a review of core processes. *Annu. Rev. Psychol.* **58**, 259–289 (2007).
104. Parvizi, J., Van Hoesen, G. W., Buckwalter, J. & Damasio, A. Neural connections of the posteromedial cortex in the macaque. *Proc. Natl Acad. Sci. USA* **103**, 1563–1568 (2006).
105. Vincent, J. L. *et al.* Intrinsic functional architecture in the anaesthetized monkey brain. *Nature* **447**, 83–86 (2007).
106. Orfei, M. D. *et al.* Anosognosia for hemiplegia after stroke is a multifaceted phenomenon: a systematic review of the literature. *Brain* **130**, 3075–3090 (2007).
107. Gray, M. A., Harrison, N. A., Wiens, S. & Critchley, H. D. Modulation of emotional appraisal by false physiological feedback during fMRI. *PLoS ONE* **2**, e546 (2007).
108. Kringelbach, M. L. The human orbitofrontal cortex: linking reward to hedonic experience. *Nature Rev. Neurosci.* **6**, 691–702 (2005).
109. Semendeferi, K. & Damasio, H. The brain and its main anatomical subdivisions in living hominoids using magnetic resonance imaging. *J. Hum. Evol.* **38**, 317–332 (2000).
110. Schweinhardt, P. *et al.* An fMRI study of cerebral processing of brush-evoked allodynia in neuropathic pain patients. *Neuroimage* **32**, 256–265 (2006).
111. Eisenberger, N. I., Lieberman, M. D. & Williams, K. D. Does rejection hurt? An fMRI study of social exclusion. *Science* **302**, 290–292 (2003).
112. Roy, M., Peretz, I. & Rainville, P. Emotional valence contributes to music-induced analgesia. *Pain* **134**, 140–147 (2008).
113. Droit-Volet, S. & Meck, W. H. How emotions colour our perception of time. *Trends Cogn. Sci.* **11**, 504–513 (2007).
114. Naidich, T. P. *et al.* The insula: anatomic study and MR imaging display at 1.5 T. *AJNR Am. J. Neuroradiol.* **25**, 222–232 (2004).
115. Augustine, J. R. The insular lobe in primates including humans. *Neurol. Res.* **7**, 2–10 (1985).
116. Augustine, J. R. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res. Brain Res. Rev.* **22**, 229–244 (1996).
117. Mufson, E. J., Sobreviela, T. & Kordower, J. H. in *Handbook of Chemical Neuroanatomy, Vol. 13: The Primate Nervous System, Part I*. (eds Bloom, F. E., Bjorklund, A. & Hokfelt, T.) 377–454 (Elsevier Science, 1997).
118. Ture, U., Yasargil, D. C., Al Mefty, O. & Yasargil, M. G. Topographic anatomy of the insular region. *J. Neurosurg.* **90**, 720–733 (1999).
119. Olausson, H. *et al.* Unmyelinated tactile afferents signal touch and project to insular cortex. *Nature Neurosci.* **5**, 900–904 (2002).
120. Olausson, H. *et al.* Feelings of warmth correlate with neural activity in right anterior insular cortex. *Neurosci. Lett.* **389**, 1–5 (2005).
121. Small, D. M., Zatorre, R. J., Dagher, A., Evans, A. C. & Jones-Gotman, M. Changes in brain activity related to eating chocolate: from pleasure to aversion. *Brain* **124**, 1720–1733 (2001).
122. Veldhuizen, M. G., Bender, G., Constable, R. T. & Small, D. M. Trying to detect taste in a tasteless solution: modulation of early gustatory cortex by attention to taste. *Chem. Senses* **32**, 569–581 (2007).
123. Frank, G. K. *et al.* Sucrose activates human taste pathways differently from artificial sweetener. *Neuroimage* **39**, 1559–1569 (2008).
124. Wang, G. J. *et al.* Gastric distention activates satiety circuitry in the human brain. *Neuroimage* **39**, 1824–1831 (2008).
125. Leibenluft, E., Gobbini, M. I., Harrison, T. & Haxby, J. V. Mothers' neural activation in response to pictures of their children and other children. *Biol. Psychiatry* **56**, 225–232 (2004).
126. Bartels, A. & Zeki, S. The neural correlates of maternal and romantic love. *Neuroimage* **21**, 1155–1166 (2004).
127. Johnstone, T., van Reekum, C. M., Oakes, T. R. & Davidson, R. J. The voice of emotion: an fMRI study of neural responses to angry and happy vocal expressions. *Soc. Cogn. Affect. Neurosci.* **1**, 242–249 (2006).
128. Takahashi, H. *et al.* Brain activations during judgments of positive self-conscious emotion and positive basic emotion: pride and joy. *Cereb. Cortex* **18**, 898–903 (2008).
129. Ortigue, S., Grafton, S. T. & Bianchi-Demicheli, F. Correlation between insula activation and self-reported quality of orgasm in women. *Neuroimage* **37**, 551–560 (2007).

Acknowledgements

I thank J. Allman, L. Feldman Barrett, P. Churchland, M. Paulus and I. Strigo for their comments on the manuscript, and Professor T. P. Naidich for supplying the photograph in figure 1. I am grateful for funds from the James S. McDonnell Foundation and for continuous support from the Barrow Neurological Foundation.

FURTHER INFORMATION

A. D. (Bud) Craig's homepage: http://www.thebarrow.org/Research_and_Clinical_Trials/Basic_Research_Laboratories/Atkinson_Pain_Research_Lab/index.htm

National Geographic film on elephant song: http://ngm.nationalgeographic.com/ngm/0510/feature5/audio.html

SUPPLEMENTARY INFORMATION

See online article: S1 (table)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

OPINION

Brain banking: opportunities, challenges and meaning for the future

Hans Kretzschmar

Abstract | Brain banks collect post-mortem human brains to foster research into human CNS function and disease. They have been indispensable for uncovering the secrets of many diseases, including Alzheimer's and Parkinson's. At a time when there are so many open questions in neuroscience and the incidence of brain diseases continues to increase in parallel with the aging of the population, brain banking remains at the heart of brain research. However, the major source of brain banks, the clinical autopsy, is rapidly falling into limbo. New strategies, including donor programmes, medico-legal autopsies and banking in networks, as well as fresh considerations of the ethics and public relations, are required.

When, in 1906, Alois Alzheimer first observed the characteristics of the disease that was to bear his name, he did so using silver-impregnated tissue sections of a formalin-fixed brain[1]. He described argyrophilic senile plaques and neurofibrillary tangles (NFTs). The biochemical nature of these structures remained enigmatic for decades, until amyloid-β (Aβ), the major component of senile plaques, was isolated from human brain tissue that had been neuropathologically well characterized and frozen unfixed after autopsy[2,3]. A spate of biochemical and molecular-biological work led to the discovery of amyloid precursor protein (APP), APP mutations associated with familial Alzheimer's disease (AD), and the metabolism of APP, as well as to the creation of transgenic animal models for AD and the development of therapeutic strategies. Over