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Perspective:

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

The anterior insular cortex (AIC) is implicated in a wide range of conditions and behaviors, from bowel distension and orgasm, to cigarette craving and maternal love, to decision-making and sudden insight (“aha!”) . 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 reviewed the phylogenetically novel primate lamina I spinothalamocortical pathway, which provides a primary interoceptive representation of the physiological condition of the body in the posterior insular cortex¹. The evidence at that time indicated that the anterior insular cortex (AIC) 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 surfeit of convergent data that support and extend these proposals. In this Perspective, I review recent functional imaging reports that describe activation of the AIC and I highlight those which 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. Selected studies are highlighted and others are listed in the Supplementary Tables. In most, but not all of these studies, the AIC and the anterior cingulate cortex (ACC) are conjointly 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 (see Box 1). The studies that reported activation of the AIC but not the ACC are explicitly noted. In addition, activation in the AIC often overlaps into the frontal operculum and the neighboring inferior frontal gyrus (IFG), consistent with the distribution of Von Economo neurons (VENs) in this so-called “fronto-insular” junction (see Box 2).

Interoception. Interoceptive stimuli that have been shown to activate the AIC include thirst, dyspnea, ‘air hunger’, the Valsalva maneuver, sensual touch, itch, penile stimulation, sexual arousal, cool, warm, exercise, heartbeat, wine-tasting by sommeliers, and distension of the bladder, stomach, rectum, or esophagus (see Supplementary Table). Our original 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 side², suggestive of a posterior-to-mid-to-anterior pattern of integration of interoceptive information. Here, I highlight 3 reports that substantiate and expand these findings. Critchley et al. reported fMRI and morphometric data indicating a specific role of the right AIC in heartbeat awareness³, an interoceptive measure that is correlated with individual subjective emotional awareness⁴. 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 ACC⁵; 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 (see Box 3). Finally, activation was observed in the bilateral AIC (R>L) during non-painful esophageal distention or viewing of fearful faces, and such activation displayed synergistic enhancement when these stimuli were delivered simultaneously⁶, 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. 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 stimulation were associated with activation of the bilateral AIC but not the posterior insula⁹. 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, neighboring sites of activation in the AIC that were somatotopically arranged¹⁰.

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 in the bilateral mid-insula. Another study reported activation in the right mid-insula (y=-10) during the rubber hand illusion, in which the subject was not actually moving but felt like the moving hand was her/his own¹³. 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 region¹⁴. 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 ‘my’ movements in an emotional present as part of a representation of all feelings from the body.

Self-recognition. The imaging studies cited in the Supplementary Table reported that the act of seeing one’s own image produced activation in the AIC. The most recent study¹⁵ 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 visual self-recognition of either body part they found selective activation of the AIC and the adjacent inferior frontal gyrus (IFG) and the 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 the Supplementary 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 (but 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 side¹⁷. One review presented evidence that the AIC is activated bilaterally during overt speech and singing, and most strikingly, that the AIC activation is asymmetric during covert singing --- activity in the right AIC was higher during slower tempos (<3Hz),

and activity in the left AIC was higher during faster tempos (>3Hz)¹⁸.

Emotional awareness. Almost all recent imaging studies of emotion report conjoint 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 only in association with subjective feelings from the body, but rather 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 hypothalamus¹⁹. 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 for the influence of emotion on cognition. In addition, several studies (e.g., Refs 21, 22) found selective activation in overlapping regions in the AIC during an empathic feeling and a comparable subjective feeling (e.g., seeing disgust expressed on another’s face and smelling a disgusting odor), with the former located anterior to the latter (consistent with the posterior-to-anterior gradient towards greater behavioral complexity in frontal cortex²⁰). Notably, similar locations in the AIC may be active during quite different emotions and behaviors²¹⁻²³; across all studies, a main determinant of location within 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).

Risk, uncertainty, and anticipation. Of the articles listed in the Supplementary 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 AIC²⁴; another study (in which this learning model was adapted for neuroeconomic studies) reported that both the risk prediction and risk-prediction error signals specified in the model are present only in the bilateral AIC²⁵. 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 decisions²⁶.

Visual and auditory awareness of the moment. Several reports that associate activation in the AIC with awareness of sensory bistable percepts must be explicitly noted here²⁷⁻²⁹, but I highlight three additional studies. The first is a PET study which described 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 (e.g. a speaking mouth)³⁰. The second is an fMRI study which examined “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 msec, 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 study³² used the attentional blink paradigm, in which a second target cannot be perceived if it occurs too quickly following a primary target in a rapid series of visual stimuli. The authors reported conjoint activation of the AIC/IFG and the ACC (plus DLPFC + parietal regions) when the second target was correctly detected at the shortest intervals (100-200 msec) 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. Conjoint activation in or near the AIC and the ACC has been reported in many studies of 'mental timekeeping' and interval estimation across the range of seconds to sub-seconds, but little explanation has been given for this activity (e.g., Ref. 33). In a recent report, task difficulty was manipulated in order to isolate time estimation from other task-related cognitive demands³⁴. 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 (e.g., Ref. 35), and some have argued that attention and consciousness must be different processes³⁶. 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 prior to 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 attention³⁷. 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 (see 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 in the ACC. In another study, a well-practiced behavioral 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 ACC³⁸. 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.⁴⁰ 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, confluent with the awareness of the percept itself. Second, Thielscher and Pessoa³⁹ 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 '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, the accessibility or the 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 report described functional connectivity analyses that were performed on brain activation during a combined working memory / target-switching task; a 'cognitive-control network' was identified that includes the bilateral AIC and the ACC⁴³. In another report, brain activation was analyzed during a variety of 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 behavior and sensory processing⁴⁴. A study of the willed inhibition of movement (using a stop-signal paradigm in which the subjects voluntarily initiated an intentional hand movement but on signaled 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 they called “free won’t”, as opposed to free will)⁴⁵. The authors associated the AIC activation with the affective consequence of canceling a motor intention (‘frustration’), and other investigators in similar studies associated such activation with autonomic arousal⁴⁶. 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 indeed found for the AIC⁴⁶ and the MPFC region⁴⁵ in these studies. 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 above³⁷, and then independent component analyses and backward deconvolutions were performed to identify brain activation patterns that preceded errors⁴⁷. 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 above³⁷. These results are therefore also consistent with the alternate interpretation that the AIC activity represents awareness and that the ACC activity represents the control of directed effort. A very 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, demonstrated 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 network⁴⁸.

Finally, the study by Klein et al.²³ may provide direct evidence that the AIC engenders awareness. They used an antisaccade task with a distractor (in which subjects were instructed to shift their gaze in the direction opposite a briefly displayed indicator, but were occasionally misdirected by an intervening precue that indicated the other direction), which produced occasional erroneous saccades that the subjects were either aware of (and signaled with a button press) or were 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 sub-threshold). 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 response²³. They recommended the use of EEG recordings to resolve this uncertainty, because the temporal resolution of fMRI cannot.

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 with awareness of sensations and movements^{2, 3, 11-14}, of visual and auditory percepts^{27-29, 31, 32}, of the visual image of the self¹⁵, and of the reliability of sensory images³⁰ and of subjective expectations^{24, 25}, and of the trustworthiness of other individuals (see Ref. 1). In several key experiments, the AIC was activated without apparent activation in the ACC^{11-14, 16, 23, 24, 25, 34}. No other region of the brain is activated in all of these tasks, and the only feature 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 ‘me’ as a feeling (sentient) entity, second, a mental representation of that object, and third, a mental representation of the salient interrelationship between me and that object in the immediate moment (‘now’)^{49, 50}. As in Damasio’s “neural self”⁵¹, this formulation inherently creates a subjective (“personal”⁵¹) perspective that differentiates inner and outer realms, because the inner feelings that underlie the representation of “me” as a sentient being are only accessible from the owner’s brain^{51, 52}. In this view, one can lose the ability to perceive a portion of extrapersonal space (e.g., following damage to right parietal cortex) or 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 (e.g., the patient with only visceral feelings remaining and an intact anterior insula⁵¹, or patient R.B., who lives in a moving 40-sec window of present time^{51, 52}). A further proposal is that a reflective awareness of ‘me’ across time that can compare the effects of my actions now, in the past and in the future was required for the evolution of deliberate social signalling, or 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 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 this test has validity as a sufficient but not necessary criterion⁵⁴ [+ new refs DeWaal 2008, Reiss and Marion 2001 and Prior et al 2008]; 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 wagering⁵⁵.

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 “my feelings” (i.e., the sentient self) is now well documented and supports the proposition that subjective awareness is built upon homeostasis^{1,4,51}. The noted studies on the perception of bistable percepts²⁷⁻²⁹, time synchronization³⁰, inspection time³¹, the attentional blink³², 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 test¹⁵, 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”⁴¹ suggests that the AIC also engenders awareness of feelings that are associated with mental constructs and operations (see Refs 56, 57).

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 time³⁴, it is sensitive to time synchronization³⁰, and it is uniquely involved in automatic comparisons of feelings in the present moment with those in the past and the future²⁵. These findings also indicate that the AIC incorporates a ‘buffer’, or comparator, that is used for such comparisons. These observations suggest that the AIC fulfills 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 [new ref James 1890/2008] for “consciousness”.) Significantly, the evidence that the AIC is also associated with predictions of future feelings can explain the involvement of the AIC in the distorted interoceptive predictions that are associated with anxiety and functional somatic disorders^{58,59}.

The findings I highlighted on perceptual decision-making (“choice”)³⁹ and cognitive control (“free won’t”⁴⁵; preparation for error commission⁴⁷; attentional transitions⁴⁸) imply that the AIC has a role in the subjective guidance of mental and physical behavior. 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. 60). Such involvement does not contradict the idea that the ACC subserves volitional agency (see Box 1), which is supported by its conjoint (with the AIC) activation in almost all of these studies and its association with action and the descending limbic motor system⁶¹.

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. The Supplementary 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 fronto-temporal dementia (FTD). Many of these reports are quite narrowly focused and do not describe comprehensive behavioral 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 (a lack of awareness of an impairment in limb movement) is specifically associated with damage in the right mid-insula^{62,63}; adolescents with conduct disorder were found to have a significant decrease in gray matter volume in bilateral AIC that correlated with lack of empathy and aggressive behavior⁶⁴; 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 subjects⁶⁵; high-functioning autistic people 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) (Ref. 66; compare Refs. 67, 68); hyperactivity in the right AIC was selectively associated with anxiety⁵⁸; infarcts of the AIC were reported to produce anergia, or complete listlessness

⁶⁹; and congenital malformation of the bilateral insula (Smith-Magenis syndrome) produces childhood mental retardation and the disruption of self-guided behavior ⁷⁰. Most significantly, fronto-temporal dementia (FTD) patients with degenerate fronto-insular and cingulate cortices display a selective loss of self-conscious behaviors and a loss of emotional awareness of self and others ⁷¹; in fact, Seeley et al. (2006) reported the landmark finding that the loss of subjective emotional awareness in FTD patients is specifically associated with the degeneration of VENS ⁷². These reports are especially notable in light of the obvious difficulties in demonstrating deficits in emotional awareness in adult humans who have well-established behavioral patterns.

Thus, the available data provide compelling support for the concept that the AIC contains the anatomical substrate for the evolved capacity of humans for awareness of themselves, others and the environment. In my opinion, these data suggest that the AIC uniquely fulfills 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 (see Refs. 73 and 63). Nevertheless, the evidence suggests that the AIC and the adjoining frontal operculum (on both left and right sides) contains an ultimate representation of the sentient self in humans (and perhaps humanoid primates, elephants and whales; see Box 2). These data recommend discussion of the possibility that the AIC is a ‘neural correlate of consciousness’ (cf. Ref. 73) and of the question of how the AIC might engender awareness.

A model for awareness in the AIC

In a recently published book chapter ⁷⁴, 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 for a role of 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, 74}.

The phylogenetically novel 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 posterior insular cortex¹; 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; see 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 (nucleus accumbens)⁷⁵, which provides an important incentive / 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 frontal cortex^{20, 61} and with the enormous expansion of anterior insula across humanoid 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 (see Figure 3B).

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 within a finite present⁷⁴ (Figure 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 based on acquired internal models of one’s own and others’ behavior. 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 (see 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 humanoid primates [new ref Dunbar and Schultz 2007] - and that each stage would have been easily realizable by evolutionary neuroanatomical modifications.

Implications and future directions

It is fascinating that the hypothesized 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 and by musical enjoyment, 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 period⁷⁶. 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 (Figure 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 Hz³¹. A similar process for the recruitment of global emotional moments could provide the basis for “heightened awareness” of the immediate moment and 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 agent⁷⁷, so that each global emotional moment comprises both feelings and motivations (see Box 1). Indeed, the representation within the sentient self of the active behavioral agent (the “I”) fills a gap in the ‘somatic marker’ hypothesis⁵¹ and it challenges a main criticism of the James-Lange theory⁵¹, viz., 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^{56,57}.

Finally, this model includes the possibility that emotional behaviors 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 as we are (see Box 2), and it provides a ready basis for the inclusion of a module that would assign responsibility for the behavioral agent's actions to the sentient self⁶⁰.

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 heartbeat), the mechanism for shifting moments across time, the neural metric of salience, the differentiation of emotions, the necessary dynamic connectivity of global emotional moments⁷⁸, or the integration between the two sides (see Box 3). It does not specify the location of memories of past feelings or the location of the internal behavioral 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, based on their intimate connectivity (for example, see the contrasting results in the literature on alexithymia). I look forward particularly to the future identification of the various functional modules within the AIC and of 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.

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Box 1. The co-activation of AIC and ACC.

It is understandably mystifying that a region of ventrolateral prefrontal cortex (AIC) and a region of medial prefrontal cortex (ACC) are co-active in so many behaviors, 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 Saper⁸⁰⁻⁸², while the medial prefrontal cortex has been associated with conflict responses, impulsive behavior, and autonomic activity.

In an earlier article I suggested that the insula and the ACC be regarded as limbic sensory and motor

cortices that engender the feeling and the motivation (agency), respectively, that constitute each emotion¹. 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 gray) brainstem regions, the overall anatomical organization of frontal cortex into sensory and motor networks, and the evolutionarily ancient limbic role of cingulate cortex in integrated behavioral control. I regarded the AIC as the probable site for awareness based on the afferent representation of the “feelings” from the body, and the ACC as the probable site for the initiation of behaviors. A recent review⁸³ 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 behavior in mammals. The insula evolved later for cortical processing of homeostatic sensory activity within the individual animal. The two regions became linked naturally for integrative autonomic control, and, in mammalian evolution, the insula grew as limbic behavioral activity became aligned more with autonomic activity than with olfactory activity. This anatomical perspective was illustrated in the ventral view of the brain shown here, which reveals the common relationship of these structures to the olfactory epithelium. (After Ref. 83).

Box 2. VENs and awareness.

An extraordinary morphological characteristic of the anterior insular cortex (AIC) and the anterior cingulate cortex (ACC) in humanoid primates is the unique concentration of clusters of large spindle-shaped neurons amongst the pyramidal neurons in layer 5, called von Economo neurons (VENs) after an early neuroanatomist^{84,85}. Their connections are not known, but I have proposed⁷⁴ that VENs are the substrate for fast interconnections between the physically separated advanced limbic sensory (AIC) and motor (ACC) cortices. Analogous to the tight interconnections between the contiguous somatosensory and motor cortices (so-called “U-fibers”) needed for manual dexterity (for example, for playing an instrument), the VENs might enable fast, highly integrated representations of emotional moments and behaviors. They may underlie the conjoint activity in the AIC and the ACC reported in most studies. The loss of emotional awareness and self-conscious behaviors in FTD patients that correlates with the degeneration of VENs directly supports this notion^{71,72,86} [new ref Seeley et al 2007 Alz Dis Assoc Dis].

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 monkeys⁸⁵. This trenchant phylogenetic progression parallels the results of the mirror test for self-

awareness² [new ref DeWaal 2008]. VENS have recently been reported in elephants⁸⁷ and whales⁸⁸. The possibility that this implies sentience in these animals received support recently when elephants were reported to pass the mirror test⁸⁹. Interestingly, there are reports that elephants sing or make music communally, [new ref <http://ngm.nationalgeographic.com/ngm/0510/feature5/audio.html>] 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. In contrast, while most people feel that particular dogs and cats have some sense of awareness, their cortex 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 primates¹. 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 as in humans¹. Rats and lizards apparently do not have a homologous anatomical substrate at all¹.

Box 3. Forebrain asymmetry of emotion.

There are two sides of the brain, so if there are separate time-based representations of the sentient self that subserve awareness in the AIC on both left and right sides, how are they coordinated to generate one unified self? The homeostatic model of awareness presented in this and prior articles^{1,74} suggests that there is an optimally energy-efficient 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) behavior, and individual-oriented (survival) emotions, and in the left side with energy nourishment, parasympathetic activity, relaxation, approach (appetitive) behavior, and group-oriented (affiliative) emotions. This proposal is described in detail in prior articles^{74,90}. 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 psychophysical literature indicating that the left and right forebrain halves are differentially associated with positive and negative affect⁹¹, and importantly, with the anatomical and functional asymmetry in the homeostatic afferent input to the insular cortex^{5,92,93} and in forebrain cardiac control⁹⁴. It can explain why under particular conditions the AIC is more active on one side (as illustrated in Figure 2) but also why in most conditions both sides display conjoint activity, which mirrors the coordinated sympathetic / 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 (e.g., activation of vagal afferents by gastric distension, slow breathing, or electrical stimulation) can reduce negative emotions (e.g., pain). Given the many asymmetries in the activations of the AIC noted above, 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 were sectioned^{95,96}.

Box 4. Alternate perspectives.

There are many alternate views of the neural substrates involved in human awareness or consciousness. Two particular viewpoints suggest that the ACC has a singular role in the representation of the self and emotional awareness of internal processes^{97,98}, but neither has incorporated the anatomical perspective that the AIC and the ACC are complementary limbic regions nor the evidence reviewed here.

Some investigators suggest that the posteromedial cortex (including the cingulate and the precuneus) provide the basis for self-awareness (e.g., Ref, 99). However, these areas are part of the so-called “default network”, which seems to be involved in self-reflective episodic memory retrieval and is anti-correlated in functional imaging studies with the activation in the AIC associated with awareness and task-related attention^{44,86}. The default network also seems to be present in the macaque monkey¹⁰⁰.

There are numerous proposals for the neural basis for various forms of the clinical syndrome of anosognosia, but these are complicated by the multiple levels of integration required for each perceptual capacity and by confounding issues in the clinical documentation^{63,101}. Recent clinical and anatomical correlations in patients with anosognosia for hemiplegia and hemianesthesia have focused on the insula^{62,63}. 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^{62,63,101}, although this idea remains to be tested.

Several authors suggest the existence of different levels of awareness or consciousness^{51,66,102}. Although this view is not incompatible with the present hypothesis, because more than one conceptual level of awareness may be instantiated in the AIC (including a comparator that could feel like an “observer”), other investigators might regard this as unlikely, because they prefer the notion that consciousness depends on recurrent activity within a distributed network across the entire brain (e.g., Ref. 73). For example, one author suggested that the orbitofrontal cortex is part of a global workspace that underlies consciousness¹⁰³, though its role in hedonic valuation (especially for feeding behavior) is well-developed in all mammals and it is not disproportionately enlarged in humans¹⁰⁴. 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 within the AIC that, as they proceed from posterior to anterior, have increasing complexity and that could accommodate higher levels of abstraction^{20, 22, 78, 105}. For example, although the “hurt” 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 anterior¹⁰⁶.

Box 5

Future research questions following from the model

1) What are the anatomical connections of the AIC? Modern imaging studies using DSI and functional and effective connectivity analyses are needed that incorporate its dynamic connectivity⁷⁸.

Comprehensive analysis of the hodology of the macaque insular cortex using classic tract-tracing methods also needs to be done.

2) How do the AIC on the two sides differ, and how do they interact? Direct statistical comparisons of laterality in activation blobs 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 modulation of pain by pleasant music⁷⁹.

3) Is there one somatotopic map that provides a common resource pool of “global emotional moments” and 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, the evidence suggests that eye and face are represented in the anterior-ventral AIC and hand and 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 reversed¹⁰.

4) Similarly, is there only one module in each AIC that represents time, as suggested by the tiny blobs illustrated in one study³⁴? And does the activity in this blob correlate with subjective time dilation? Are these blobs asymmetric on the two sides with respect to the contrasting effects of arousal and pleasant mood? [new ref Droit-Volet and Meck 2007]

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

6) 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?

- 7) Does emotional congruence between individuals reflect homeostatic resonance?
- 8) Do elephants really make infrasonic music together? What about whales?
- 9) Infants do not pass the mirror test or show self-conscious behaviors until about 18 months^{50, 53}. Does the connectivity of their AIC and ACC show a similar developmental threshold?
- 10) The activation of the AIC or the ACC has been used for biofeedback training. Could this application be refined in light of these considerations?

Figure Legends

Figure 1. **Anatomy of the insula**

Photograph of the left insular cortex of one human patient (reproduced from Naidich et al 2004, Ref. 107) For a direct comparison with the insulae of two other patients, see the original publication.

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 monkey¹⁰⁴. It has 5-7 oblique gyri, but its morphology is quite variable, even between the two sides¹⁰⁷⁻¹¹¹. 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 AIC^{2, 7, 112, 113}. 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^{92, 114-117}, 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 ACC; see Box 1) contains von Economo neurons (VENs) (see Box 2).

Figure 2. **Activation of the AIC**

Summary figure of imaging results showing activation of the AIC during particular tasks and emotions highlighted in the text and indicated in the figure. The two columns at the right show activation predominantly on the right side or the left side from different studies. Stimuli that activate the right AIC are generally arousing to the body, like pain. The left AIC is activated predominantly by positive and affiliative emotional feelings (see Box 3). For example, activation in the AIC on the left side was reported in mothers viewing photos of their own child¹¹⁸; activation of the AIC (L>R) was associated with both maternal and romantic love¹¹⁹; activation in 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 ¹²⁰; activity in the left AIC was associated with hearing pleasant music ¹⁷; selective activation of the left AIC was observed in subjects experiencing joy ¹²¹; and, selective activation of the left AIC was found in females that correlated with self-reported orgasm ratings ¹²². The sources for the images shown are (listed in order from top to bottom and from left to right): Ref. numbers 23, 45, 40, 39; next column, 41, 31, 34; next column, 2, 7, 3, 24, 15; next column, 17, 16, 118, 120, 21.

Figure 3. **A proposed model of awareness**

Cartoons illustrating features of the proposed structural model of awareness. **A.** The upper left panel shows the hypothesized integration of salient activity progressing from the posterior (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, indicated by the focus of the colors 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 upper right panel shows how a series of global emotional moments can produce a cinemascopic “image” of the sentient self across time. The lower right panel shows how this structure can produce a subjective dilation of time during a period of high emotional salience, when global emotional moments are rapidly “filled up”.

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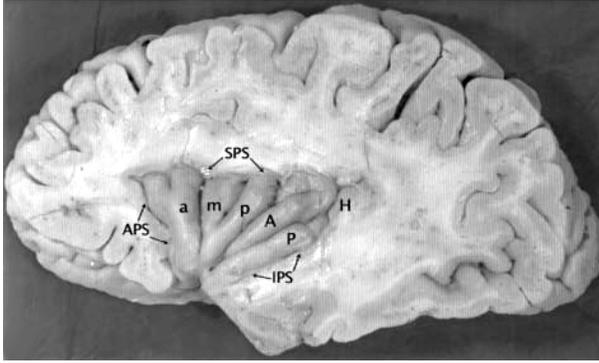


Fig. 1

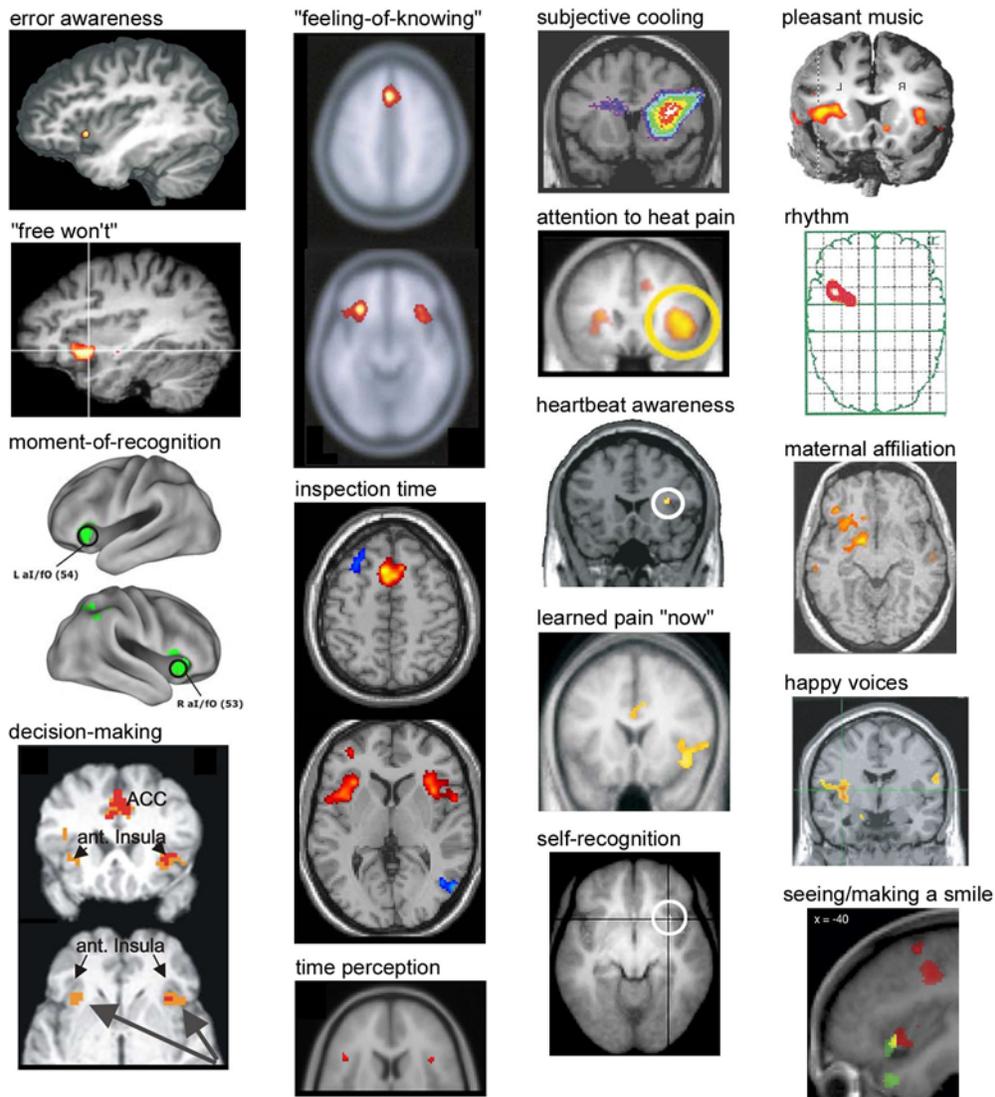


Fig. 2

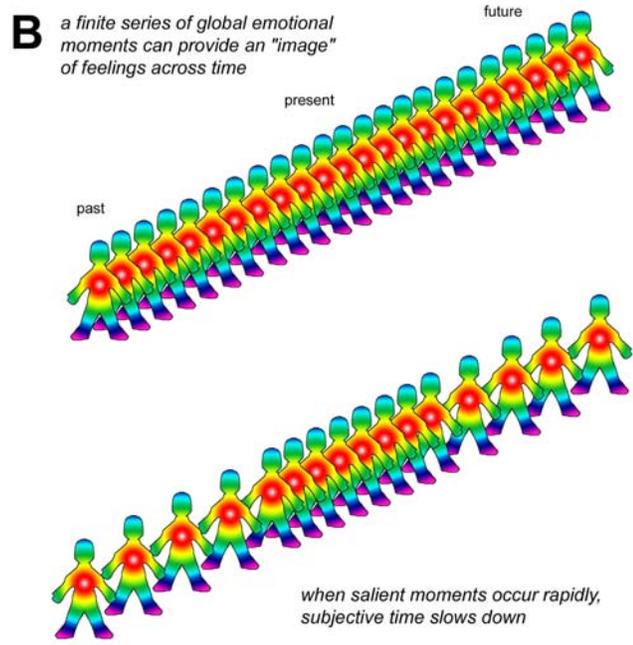
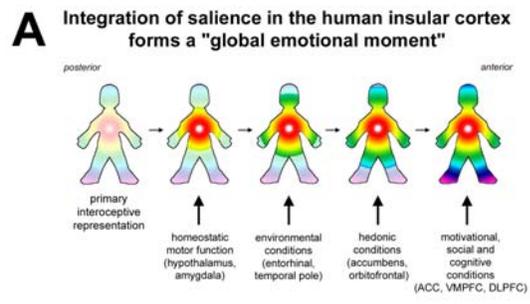


Fig. 3