

# Anterior Insular Cortex and Emotional Awareness

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## ABSTRACT

This paper reviews the foundation for a role of the human anterior insular cortex (AIC) in emotional awareness, defined as the conscious experience of emotions. We first introduce the neuroanatomical features of AIC and existing findings on emotional awareness. Using empathy, the awareness and understanding of other people's emotional states, as a test case, we then present evidence to demonstrate: 1) AIC and anterior cingulate cortex (ACC) are commonly coactivated as revealed by a meta-analysis, 2) AIC is functionally

dissociable from ACC, 3) AIC integrates stimulus-driven and top-down information, and 4) AIC is necessary for emotional awareness. We propose a model in which AIC serves two major functions: integrating bottom-up interoceptive signals with top-down predictions to generate a current awareness state and providing descending predictions to visceral systems that provide a point of reference for autonomic reflexes. We argue that AIC is critical and necessary for emotional awareness. *J. Comp. Neurol.* 521:3371-3388, 2013.

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**INDEXING TERMS:** anterior insular cortex; emotional awareness; empathy; fMRI; meta-analysis; top-down; bottom-up; predictive coding

## NEUROANATOMICAL FEATURES OF THE INSULAR CORTEX

The human insular cortex was first described by Johann-Christian Reil in 1796 and has since been known as the *island of Reil* (for review see Binder et al., 2007). It lies in the depth of the lateral sulcus and can be directly observed only by removal of the overlying frontal and temporal lobes (Naidich et al., 2004). The insula has widespread connections with other parts of the brain (Saper, 2002). In rats, the insular cortex is interconnected with the autonomic system as well as limbic and frontal regions (Saper and Loewy, 1980; Saper, 1982; Allen et al., 1991) and has been shown to contain a viscerotopic map (Cechetto and Saper, 1987). It also receives projections from the glossopharyngeal nerve in rabbits (Yamamoto and Kawamura, 1975). Insular neurons respond to stimulation of the cervical vagus nerve in squirrel monkeys (Radna and MacLean, 1981). In humans, the insula has bidirectional connections with the frontal, parietal, and temporal lobes; the cingulate gyrus; and subcortical structures such as the amygdala, brainstem, thalamus, and basal ganglia (Flynn et al., 1999). These connections serve as

the anatomical foundation for the integration of autonomic, viscerosensory, visceromotor, and limbic functions in the insular cortex.

Cytoarchitecturally, the insular cortex is roughly divided into an anterior agranular portion (anterior insula, AIC), a middle dysgranular portion (middle insula), and a posterior granular portion (posterior insula) in both humans (Flynn et al., 1999; Butti and Hof, 2010; Bauernfeind et al., 2013; Butti et al., 2013) and macaque monkeys (Mesulam and Mufson, 1982a), although more subdivisions have been revealed in monkeys recently (Gallay et al., 2012; Evrard H, Logothetis NK, Craig AD, in press). Each subdivision has its own unique connectivity and functional features. The posterior insula receives spinal

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lamina I afferents via the brainstem and thalamic nuclei and is largely linked to brain region involved in somato-motor functions; the agranular AIC is connected predominantly with allocortical areas and integrates autonomic and interoceptive information (Flynn et al., 1999). The insula, and especially the agranular AIC, is also among the most differentially expanded neocortical regions in humans compared with other primate species (Bauernfeind et al., 2013). Another distinguishing feature of AIC is that it contains a special group of large, bipolar, spindle-shaped neurons referred to as von Economo neurons (VENs; von Economo, 1926; Seeley et al., 2012). To date, VENs have been found to exist only in humans and great apes (Nimchinsky et al., 1995, 1999; Allman et al., 2010), macaque monkeys (Evrard et al., 2012), cetaceans and a number of their related terrestrial herbivore species (Hof and Van der Gucht, 2007; Butti et al., 2009, 2013; Butti and Hof, 2010), and elephants (Hakeem et al., 2009). They are most abundant in humans and are found primarily in layer Vb in the anterior cingulate cortex (ACC; Nimchinsky et al., 1995) and in the junction of the posterior orbitofrontal cortex and AIC known as the fronto-insular cortex (Allman et al., 2010). VENs are projection neurons approximately 4.6 times the size of neighboring pyramidal neurons and are considered well-suited for rapid, long-distance integration of information (Allman et al., 2005, 2010).

## EMOTIONAL AWARENESS: EXISTING FINDINGS AND THEORIES

### Conscious vs. unconscious emotional processes

We propose that the insula serves a critical role in emotional awareness. Emotion, as a multiconstrual concept, is usually considered to consist of a physiological-biological component, an experiential-psychological component, and an expressive-social component (Lane and Schwartz, 1987; Dolan, 2002). Lane and Schwartz defined five levels of emotional awareness as the awareness of bodily sensations, the body in action, individual feelings, blends of feelings, and blends of blends of feelings (Lane and Schwartz, 1987). In the current review, we simplify this definition as the conscious experience of emotions (the experiential or “feeling” domain of emotion); operationally, emotional awareness occurs during the supraliminal processing of affective stimuli (Pessoa, 2005). Compelling evidence shows that emotional perception, evaluation, and behavior can be processed with or without conscious awareness (see, e.g., Ohman and Soares, 1994) and that emotional awareness is a necessary, but not a sufficient, condition for successful emotional processing. However, it has

been suggested that only coarse affective properties can be registered without awareness (Pessoa, 2005) and that the capacity to experience emotions fully significantly increases the likelihood of one to make an appropriate action or decision (Lane and Schwartz, 1987).

### Interoception and emotional awareness

Interoception is the sense of the physiological condition of the body (Craig, 2002, 2003). The ongoing discussion on the relationship between interoception and emotional awareness can be dated back to the era of William James (1884) and Carl Lange (1885), if not earlier. Lange considers cardiovascular responses as a basis for emotional awareness, whereas James extends this view by including autonomic functions other than cardiovascular responses. Their ideas, usually mentioned together as the James-Lange theory, was challenged by the Cannon-Bard theory (Bard, 1928; Cannon, 1932), which argues that bodily responses are the result, not the cause, of emotions and that a central nervous system is needed to generate emotional feelings. The self-perception theory, derived from radical behaviorism, supports the notion that emotional feelings follow behavior, although the extent differs among individuals (Bem, 1967; Laird, 1974). More recently, it has been proposed that reactivation of bodily and neural responses involved in lower-level sensorimotor processes contributes to subjective awareness (Thompson and Varela, 2001; Niedenthal, 2007; Harrison et al., 2010; Gray et al., 2012; Oosterwijk et al., 2012; Pollatos et al., 2012). Such embodiment of high-level emotional feelings is sometimes termed the “somatic marker,” which captures the physical aspect of subjective awareness (Damasio, 1996). By incorporating ideas from theoretical neurobiology, it has recently been suggested that predictive coding of interoceptive information is important in awareness (Seth et al., 2011). This implies that emotion can be viewed as a form of interoceptive inference; that is, subjective feelings are based on the active interpretation of changes in the physiological conditions of the body (Seth et al., 2011). These new developments support an inseparable relationship between interoception and emotional awareness.

### Brain mechanisms of emotional awareness

Although several other brain regions such as ACC, amygdala, and ventromedial prefrontal cortex are commonly implicated (Lane et al., 1998; LeDoux, 2000; Cohen et al., 2001; Adolphs, 2002; Ochsner and Gross, 2005; Phelps, 2006; Duncan and Barrett, 2007; Lieberman, 2007), the insular cortex has been singled out as a critical neural substrate for interoceptive and emotional awareness (Craig, 2009, 2010, 2011; Singer et al.,

2009; Jones et al., 2010; Seth et al., 2011). The posterior insular cortex has been commonly associated with somatotopic representations of bodily states such as itch, pain and temperature, and touch (Damasio et al., 2000; Craig, 2002, 2009; Harrison et al., 2010), whereas AIC participates in a wide range of functions, including and beyond bodily representations. Neuroimaging studies consistently show that AIC activation is associated with cardiovascular functions (King et al., 1999; Henderson et al., 2002), respiration (Banzett et al., 2000; Henderson et al., 2002), pain (Treede et al., 1999; Wager et al., 2004), touch (Keysers et al., 2004; Lindgren et al., 2012), thermosensory awareness (Craig et al., 2000), disgust (Phillips et al., 1997; Wicker et al., 2003; Calder et al., 2007), interoceptive awareness (Critchley et al., 2004; Zaki et al., 2012), general emotional processing (Davidson and Irwin, 1999; Zaki et al., 2012), cognitive control (Eckert et al., 2009; Menon and Uddin, 2010), empathy (Singer et al., 2004; Gu and Han, 2007a; Gu et al., 2010, 2012, 2013; Lamm et al., 2010; Ebisch et al., 2011), intuition (Kuo et al., 2009), unfairness (Sanfey et al., 2003; Kirk et al., 2011), risk and uncertainty (Preuschoff et al., 2008; Bossaerts, 2010; Ullsperger et al., 2010; Bach and Dolan, 2012), trust and cooperation (King-Casas et al., 2008), and norm violations (Montague and Lohrenz, 2007; Xiang et al., 2013). It has also been observed that patients with focal epileptic seizures that arise from the AIC report heightened emotional awareness and enhanced wellbeing (Picard, 2013), further supporting a role of AIC in emotional awareness.

A posterior-to-anterior gradient in the insular cortex has been proposed, in which physical features of interoception are processed in the posterior insula and the integration of interoception with cognitive and motivational information in the AIC, and the right AIC serves a more dominant role than the left AIC (Craig, 2009, 2010, 2011). Recent work further suggests that, as a critical neural correlate in interoceptive predictive coding, AIC serves a computational role in emotional awareness (Seth et al., 2011). The insular cortex is therefore considered to form an interoceptive image of one's physiological states and consequently to relay internal needs to subjective awareness of feelings (Craig, 2002; Harrison et al., 2010).

It is noteworthy that the insular cortex works closely with a network of regions, including the ACC (Critchley, 2004; Critchley et al., 2004; Medford and Critchley, 2010; Fan et al., 2011; Denny et al., 2012; Lindquist et al., 2012), somatosensory cortex (Gu et al., 2013), and amygdala (Etkin and Wager, 2007). It has been pointed out that patients with bilateral insular damage still preserve certain aspects of emotional awareness, suggesting that emotional feelings might first emerge

from the brainstem and hypothalamus, which are later enriched and refined by the insula (Damasio et al., 2013).

### Clinical significance: alexithymia and related disorders

Deficit in emotional awareness, termed as *alexithymia* (Taylor, 2000), is commonly seen in conditions associated with neuropathological degeneration of the VENS and functional deficits of the AIC, such as behavioral variant frontotemporal dementia (Seeley et al., 2006; Seeley, 2010; Kim et al., 2012), callosal agenesis (Kaufman et al., 2008), and autism (Santos et al., 2011; Butti et al., 2013). Among the popular tools to measure trait alexithymia is the 20-item Toronto Alexithymia Scale (TAS-20), which assesses three aspects of emotional deficits: difficulty in identifying emotions, difficulty in describing emotions, and externally oriented thinking style (Taylor et al., 2003). As assessed by TAS-20, the prevalence of alexithymia is approximately 10% in the general population (Kokkonen et al., 2001) and is remarkably high in patients with autism spectrum disorders (85%; Hill et al., 2004). In autism, lower AIC activations are correlated with higher TAS-20 scores (Bird et al., 2010). Patients with frontotemporal dementia are more alexithymic than matched controls, and such deficits have been associated with abnormalities in pregenual ACC (Sturm and Levenson, 2011) and AIC (Seeley, 2010). Alexithymia is also observed in individuals with depersonalization syndrome (Simeon et al., 2009). Even in the absence of psychiatric or neurological disorders, alexithymia is very common among elderly people (34%; Joukamaa et al., 1996). This suggests that emotional awareness is important to mental health and that impaired emotional awareness interferes with normal social function in both clinical and nonclinical populations. Diminished ability to integrate information rapidly among spatially distinct regions may underlie functional deficits in these conditions and, ultimately, in the inability to make quick and intuitive judgments regarding uncertain and rapidly changing social contexts (Allman et al., 2005).

### EMPATHY AS A TEST CASE FOR EMOTIONAL AWARENESS

Next we review evidence supporting a critical role of AIC in emotional awareness using empathy as a test case. Empathy refers to the awareness and understanding of the sensory and emotional states of other people (Gu et al., 2012). In experimental settings, empathetic emotions are externally generated by visual or auditory affective stimuli, in contrast to self-generated emotions

induced by instructions. Empathy is closely related to, yet different from, emotional contagion, in that the latter is merely passive, whereas empathy also involves active and top-down components such as perspective taking and social understanding (Preston and de Waal, 2002; Decety and Jackson, 2004). A substantial portion of work on emotion involves visual stimuli depicting another person's emotions (e.g., facial expressions; for reviews see Davidson and Irwin, 1999; Adolphs, 2002; Phelps, 2006; Pessoa and Adolphs, 2010) because of the advantage of allowing specific yet flexible experimental manipulations (e.g., compared with somatosensory stimuli). In such studies, empathy is often involved but not explicitly discussed. In the following paragraphs, we consider four lines of evidence to support the notion that AIC is critical for empathetic emotions: 1) AIC and ACC are commonly coactivated as revealed by a meta-analysis, 2) AIC is functionally dissociable from ACC, 3) AIC integrates stimulus-driven and top-down information, and 4) AIC lesions are associated with deficits in emotional awareness.

### Coactivation of AIC and ACC: a meta-analysis on empathy

To overcome the heterogeneity in experimental methods and achieve an unbiased quantification of neural substrates underlying empathy, we first conducted a quantitative meta-analysis on 47 functional magnetic resonance imaging (fMRI) studies (see Table 1) that examined brain activations related to empathy in healthy adults using the coordinate-based meta-analysis (Salimi-Khorshidi et al., 2009) of activation likelihood estimation (ALE) approach (Turkeltaub et al., 2002; Laird et al., 2005; Eickhoff et al., 2009). This algorithm treats activated foci of brain regions as three-dimensional Gaussian probability distributions centered at the given coordinates instead of points (Laird et al., 2005; Eickhoff et al., 2009) and incorporates the size of the probability distributions by taking into account the sample size of each study and by utilizing random-effect rather than fixed-effect inference by testing the above-chance clustering between experiments/contrasts rather than the above-chance clustering between foci (Eickhoff et al., 2009).

A literature search was carried out in PubMed and Web of Science (through August, 2010, the time at which we began the meta-analysis) using any of the following indexing terms: "empathy," "empathetic," "altruism," "sympathy," "emotional contagion," "compassion," in combination with "fMRI" by four researchers independently (X.G. and three research assistants). All of the resulting 158 articles were pooled into a database, and

redundant entries were eliminated. We then excluded articles that 1) were review articles or other nonempirical studies; 2) did not report results in Talairach or Montreal Neurological Institute (MNI) space; 3) used tasks unrelated to empathetic processes and with no measurement of trait empathy; 4) were based on structural analyses only; 5) were based on region of interest (ROI) analysis (e.g., using anatomical masks or coordinates from other studies), principal component analysis, or functional or effective connectivity analysis only; 6) were based on special populations (e.g., children, aging adults, psychiatric patients, medical physicians, Buddhist meditators); and 7) focused on the cognitive aspects of understanding others' mental states (i.e., theory of mind). These criteria resulted in 47 articles with 2,029 foci, 194 contrasts, and 3,411 subjects in the final data set (see Table 1). We further conducted analyses on foci from studies or contrasts based on empathy for pain, empathy for negative emotions, and empathy for positive emotions. For example, the following contrasts were identified as empathy for pain: "main effect of pain: pain>no pain" (Akitsuki and Decety, 2009) and "other's pain>self pain" (Ochsner et al., 2008). The following contrasts were identified as empathy for negative emotions: "compassionate-sad>zcompassionate-neutral" (Kim et al., 2009), and "overlap between observing and feeling disgust" (Wicker et al., 2003). This category included 192 foci from 20 contrasts and 403 subjects. This category included 948 foci from 98 contrasts with 1,598 subjects. The following contrasts were identified as empathy for positive emotions: "overlap between sucrose-saliva and pleasant faces-neutral faces" (Jabbi et al., 2007) and "correlation of happy > neutral contrast with EQ" (Chakrabarti et al., 2006). This yielded 70 foci from nine contrasts with 157 subjects.

For the main analysis on all three emotional categories, we identified multiple regions involved in empathetic processing. These regions include AIC, ACC, middle and superior temporal gyri, somatosensory cortices (SI/SII), dorsal frontoparietal regions, medial prefrontal cortex (MPFC), amygdala, thalamus, and midbrain structures (substantia nigra and red nucleus; Fig. 1A, Table 2). Meta-analysis on empathy for pain also showed most consistent activations in bilateral insula and ACC (Fig. 1B, Table 3). Other regions include lateral PFC (LPFC), MPFC, SI, middle occipital gyrus, fusiform gyrus, inferior parietal lobule, amygdala, globus pallidus, claustrum, thalamus, and cerebellum. Empathy for negative emotions also reliably activated AIC and ACC (Fig. 1C, Table 4), in addition to LPFC, MPFC, red nucleus, substantia nigra, and putamen/caudate nucleus. Brain regions that showed consistent activation for empathy for positive emotions include AIC, SI, superior temporal gyrus,

**TABLE 1.**  
Demographics of Studies Included in the Meta-Analysis<sup>1</sup>

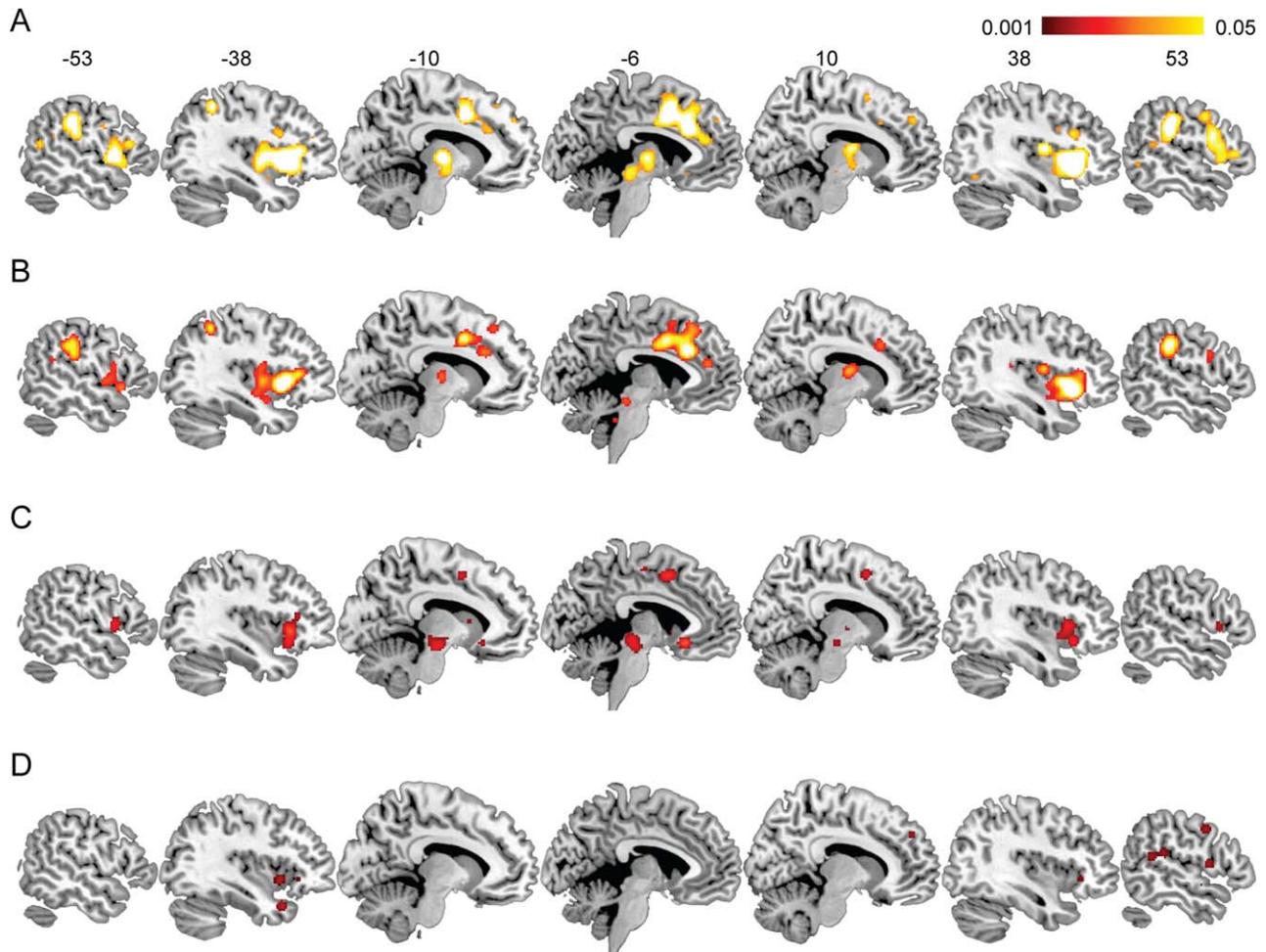
References	Sample size	Stimulus valence	Stimulus modality	Task
Akitsuki and Decety (2009)	26	Pain	Visual/image	Valence rating
Botvinick et al. (2005)	12	Pain	Visual/video	Observation
Carr et al. (2003)	11	Happy/sad/angry/surprise/disgust/ afraid	Visual/image	Imitation; observation
Chakrabarti et al. (2006)	25	Happy/sad/angry/disgust/neutral	Visual/video	Button press
Cheetham et al. (2009)	16	Pain	Visual/video	Button press
Costantini et al. (2008)	13	Pain	Visual/video	Observation
Decety et al. (2010)	22	Pain	Visual/video	Observation
Dernfl et al. (2010)	24	Happy/sad/anger/fear/disgust	Visual/image	Perspective taking
Gu and Han (2007a)	12	Pain	Visual/image	Valence rating
Gu et al. (2010)	18	Pain	Visual/image	Valence rating
Han et al. (2009)	24	Pain	Visual/video	Valence rating
Hennenlotter et al. (2005)	12	Happy	Visual/image	Imitation
Hooker et al. (2008)	20	Mixed	Visual/image	Empathizing; emotion inference
Hooker et al. (2010)	15	Mixed	Visual/image	Empathizing
Immordino-Yang et al. (2009)	13	Mixed	Auditory/Visual	Imitation
Jabbi et al. (2007)	18	Disgust/pleasant	Visual/video	Observation
Jackson et al. (2005)	15	Pain	Visual/image	Valence rating
Jackson et al. (2006)	34	Pain	Visual/image	Valence rating
Kim et al. (2009)	21	Sad	Visual/image	Empathizing; observation
King et al. (2006)	12	Pain	Visual/video	Empathetic decision making
Kramer et al. (2010)	17	Anger/sadness/pain/anxiety	Visual/image	Button press
Lamm et al. (2007a)	17	Pain	Visual/video	Perspective taking
Lamm et al. (2007b)	18	Pain	Visual/image	Valence rating
Lamm and Decety (2008)	18	Pain	Visual/image	Valence rating
Lamm et al. (2010)	24	Pain	Visual/image	Valence rating
Leslie et al. (2004)	15	Smile/frown	Visual/video	Observation; imitation
Mathur et al. (2010)	28	Pain	Visual/image	Valence rating
Morrison et al. (2004)	11	Pain	Visual/video	Observation
Morrison et al. (2007)	14	Pain	Visual/video	Observation
Morrison and Downing (2007)	16	Pain	Visual/image	Hit/miss judgment
Newman-Norlund et al. (2009)	22	Mixed	Visual/video	Hit/miss judgment
Nummenmaa et al. (2008)	10	Threat/harm	Visual/image	Empathizing
Ochsner et al. (2008)	13	Pain	Visual/video	Observation
Olsson et al. (2007)	14	Pain	Visual/video	Observation
Osborn and Derbyshire (2010)	15	Pain	Visual/image	Valence rating
Saarela et al. (2007)	12	Pain	Visual/image	Observation
Schulte-Ruther et al. (2007)	26	Angry/fearful/sad/disgusted/ happy	Visual/image	Perspective taking
Schulte-Ruther et al. (2008)	26	Angry/fearful/sad/happy	Visual/image	Perspective taking
Singer et al. (2004)	16	Pain	Visual/image	Observation
Singer et al. (2006)	16	Pain	Visual/image	Observation
Ushida et al. (2008)	15	Pain	Visual/video	Observation
van der Gaag et al. (2007)	17	Happy/disgust/fear	Visual/video	Observation; imitation
Vollm et al. (2006)	13	Mixed	Visual/image	Empathizing
Wicker et al. (2003)	14	Disgust/pleasure	Visual/video	Observation
Xu et al. (2009)	33	Pain	Visual/video	Valence rating
Zaki et al. (2007)	13	Pain	Visual/video	Observation
Zaki et al. (2009)	21	Mixed	Visual/video	Valence rating

<sup>1</sup>All references are given in the Literature Cited.

MPFC, LPFC, and inferior parietal lobule (Fig. 1D, Table 5). This category yielded fewer brain regions than previous categories, probably because of the smaller number of studies/contrasts for positive emotions. These regions largely, but not fully, overlap with the brain areas involved in empathy for pain and negative emotion.

Several aspects of these findings deserve attention. First, AIC, but not ACC, is consistently involved in the three categories of empathetic emotions examined,

suggesting a unique role of AIC in processing affective visual stimuli regardless of valence (see  $x = -38$  and  $38$  slices across Fig. 1A–D). Second, right AIC activation is absent in empathy for positive emotions and present only in empathy of pain and negative emotions, whereas left AIC is activated by all valence categories. This finding is consistent with the notion that right AIC encodes “energy-consuming” negative feelings (Craig, 2011). There are at least two possible explanations



**Figure 1.** Meta-analysis of fMRI studies of empathy processing. **A:** Empathy for all three emotions examined (pain, negative, positive). **B:** Empathy for pain. **C:** Empathy for negative emotions. **D:** Empathy for positive emotions. Color intensity represents ALE value. Note that AIC bilaterally are commonly involved in all conditions ( $x = -38$  and  $38$ ) and that ACC is involved in all but empathy for positive emotions. See Tables (2–5) for details regarding coordinates and ALE values.

regarding the function of the left AIC: 1) it directly processes both positive and negative feelings and 2) it specifically encodes “energy-nourishing” positive feelings (Craig, 2011), yet there might be asymmetrical information flow between left and right AIC such that negative feelings are processed in the right AIC first and then sent to the left AIC, a downstream region of the right AIC. Further investigations using lesion and causal modeling of neuroimaging data are needed to answer this question. Third, although we were not able to compare gender differences in the current meta-analysis, males and females have been shown to use different strategies in emotion paradigms (Baron-Cohen and Wheelwright, 2004; Singer et al., 2006; Schulte-Ruther et al., 2008). A previous meta-analysis reported that males exhibit great right AIC activation to negative stimuli (Stevens and Hamann, 2012). Finer-grained analysis on

gender differences in emotional awareness can offer insights into emotional awareness in relation to perceiver characteristics and implications for disorders such as autism (Baron-Cohen and Wheelwright, 2004).

### Functional dissociation between AIC and ACC

In line with our meta-analysis on empathy studies, it has been commonly demonstrated that AIC and ACC are coactivated in various experimental paradigms (Critchley, 2004; Dosenbach et al., 2006; Craig, 2009; Medford and Critchley, 2010; Fan et al., 2011) as well as in resting states (Seeley et al., 2007; Britz et al., 2010; Cauda et al., 2011; Fan et al., 2012). As pointed out by Craig, “it is understandably mystifying that a region of the ventrolateral prefrontal cortex (the

**TABLE 2.**  
Empathy-Related Brain Regions (All Coordinates)<sup>1</sup>

Voxel	ALE	x	y	z	Area	Label
9188	0.117	-40	14	0		L anterior insula
	0.111	38	20	-2		R anterior insula
	0.100	-46	8	4		L anterior insula
	0.070	18	8	6		R putamen
	0.068	-12	-14	4		L thalamus
	0.063	34	-6	12		R claustrum
	0.060	22	-2	-12		R amygdala
	0.058	-20	6	4		L putamen
	0.058	46	6	30	9	R inferior frontal gyrus
	0.055	-28	-4	-14		L amygdala
	0.053	4	-20	-8		R red nucleus
	0.053	-16	-8	-10		L amygdala
	0.052	0	-28	-14		Red nucleus
	0.051	-42	10	26	9	L inferior frontal gyrus
	0.049	48	2	42	6	R middle frontal gyrus
	0.048	10	-6	12		R thalamus
	0.045	-50	20	16	45	L inferior frontal gyrus
0.038	-48	-2	30	6	L precentral gyrus	
2676	0.089	-2	24	32	32	L ACC/RCZa
	0.081	-8	6	42	32	L ACC/RCZp
	0.063	0	0	38	24	ACC/CCZ
	0.051	-2	40	20	9	L MPFC
	0.041	6	48	36	6	R MPFC
	0.034	-10	50	36	8	L superior frontal gyrus
	0.033	2	-6	58	6	R MPFC
585	0.064	52	-32	30	40	R inferior parietal lobule
	0.034	50	-46	16	13	R superior temporal gyrus
522	0.066	-54	-28	36	40	L inferior parietal lobule
	0.034	-42	-36	40	40	L inferior parietal lobule
264	0.055	44	-50	-12	37	R fusiform gyrus
	0.040	48	-60	-2	19	R inferior temporal gyrus
	0.036	42	-66	-12	19	R fusiform gyrus
	0.032	50	-62	10	37	R mid temporal gyrus
157	0.053	-38	-48	50	40	L inferior parietal lobule
	0.031	-26	-60	40	7	L superior parietal lobule
140	0.039	-44	-68	-8	19	L fusiform gyrus
	0.032	-44	-70	6	37	L mid temporal gyrus
87	0.047	28	38	34	9	R mid frontal gyrus
85	0.047	32	-84	0	18	R mid occipital gyrus
55	0.035	26	-52	44	7	R superior parietal lobule
36	0.037	-50	-58	16	22	L superior temporal gyrus

<sup>1</sup> $P_{FDR} < 0.05$ ,  $k > 30$ , voxel size =  $2 \times 2 \times 2$  mm. ACC, anterior cingulate cortex; RCZa, anterior rostral cingulate zone; RCZp, posterior rostral cingulate zone; CCZ, caudal cingulate zone; MPFC, medial prefrontal cortex; L, left; R, right. RCZa, RCZp, and CCZ are defined as by Fan et al. (2008).

anterior insular cortex (AIC)) and a region of the medial prefrontal cortex (the anterior cingulate cortex (ACC)) are co-active in so many behaviors. . . .” (Craig, 2009). Indeed, ACC also has been considered a significant structure in emotional awareness (Lane et al., 1998; Lieberman, 2007). Therefore, experimental evidence showing functional dissociation between AIC and ACC is crucial in delineating the relationship between these two structures.

We recently showed a functional dissociation between AIC and ACC using an empathetic pain paradigm (Fig. 2A; modified from Gu et al., 2010, 2013). Participants were asked to judge whether the person in the pictorial stimulus is suffering from pain (“explicit” task pain; TP) or the laterality of limb (“implicit” task laterality; TL). A key

manipulation in this design is equating the cognitive load among experimental conditions. The results suggest that, after controlling for cognitive load, AIC, but not ACC, showed increased activation for painful compared with neutral pictures (Fig. 2B, modified from Gu et al., 2010). This finding points out the importance of AIC, in dissociation from ACC, in emotional awareness. In line with this evidence, several other studies have shown functional dissociation between AIC and ACC in other domains (Sridharan et al., 2008; Eckert et al., 2009). Using Granger causal analysis, Sridharan and colleagues (2008) showed that the right AIC has a causal influence on ACC and plays a critical role in switching between the central executive network and the default mode network. The

**TABLE 3.**  
Brain Regions Involved in Empathy for Pain<sup>1</sup>

Voxel	ALE	x	y	z	Area	Label
2405	0.084	-40	14	0		L anterior insula
	0.041	-30	-4	-14		L amygdala
	0.036	-16	-8	-8		L globus pallidus
	0.033	-38	-2	4		L claustrum
	0.029	-48	8	8	44	L precentral gyrus
	0.028	-46	0	24	9	L inferior frontal gyrus
	0.026	-38	-2	16		L posterior insula
2298	0.084	40	20	-4	47	R inferior frontal gyrus
	0.032	46	28	6	13	R inferior frontal gyrus
1999	0.032	26	-2	-14		R amygdala
	0.075	-2	24	32	32	L ACC/RCZa
	0.057	0	-2	36	24	ACC/CCZ
	0.050	-8	6	40	32	L ACC/RCZp
	0.031	0	10	54	6	L MPFC
506	0.053	52	-30	34	2	R SI
408	0.047	-54	-28	34	40	L inferior parietal lobule
	0.020	-44	-38	38	40	L inferior parietal lobule
302	0.033	12	-6	12		R thalamus
154	0.041	-2	42	18	9	L MPFC
150	0.028	-42	-68	-8	19	L fusiform gyrus
	0.027	-44	-72	6	19	L mid occipital gyrus
143	0.038	-38	-48	50	40	L inferior parietal lobule
131	0.040	36	-4	14		R posterior insula
117	0.027	48	4	30	9	R inferior frontal gyrus
	0.024	44	2	42	6	R mid frontal gyrus
55	0.026	-10	-12	6		L thalamus
40	0.028	30	-82	2	18	R mid occipital gyrus
35	0.027	-30	-64	-26		L cerebellum

<sup>1</sup> $P_{FDR} < 0.05$ ,  $k > 30$ , voxel size =  $2 \times 2 \times 2$  mm. ACC, anterior cingulate cortex; RCZa, anterior rostral cingulate zone; RCZp, posterior rostral cingulate zone; CCZ, caudal cingulate zone; SI, primary somatosensory cortex; MPFC, medial prefrontal cortex; L, left; R, right. RCZa, RCZp, and CCZ are defined as by Fan et al. (2008).

**TABLE 4.**  
Brain Regions Involved in Empathy for Negative Emotions<sup>1</sup>

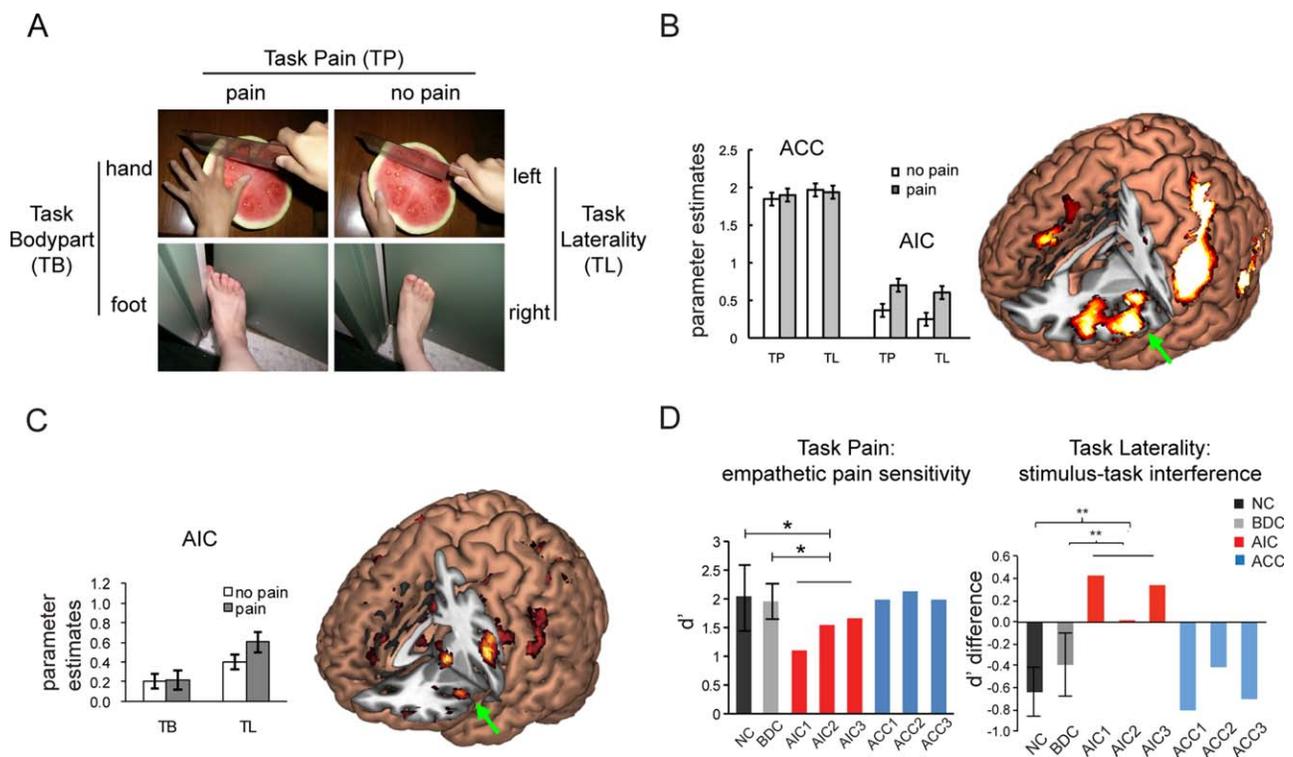
Voxel	ALE	x	y	z	Area	Label
837	0.040	-46	8	2		L anterior insula
	0.030	-42	18	-10	47	L inferior frontal gyrus
	0.028	-40	20	2		L anterior insula
650	0.019	-34	28	14		L anterior insula
	0.028	4	-18	-8		R red nucleus
	0.023	0	-26	-12		L red nucleus
	0.021	-12	-16	-12		L substantia nigra
505	0.017	6	-10	2		R thalamus
	0.034	44	16	4		R anterior insula
406	0.022	36	22	-8	47	R inferior frontal gyrus
	0.025	-2	10	50	6	L MPFC
165	0.021	6	8	50	6	R MPFC
	0.018	0	-10	56	6	L MPFC
149	0.018	-20	8	10		L putamen
	0.017	-18	4	0		L putamen
117	0.023	2	10	0		R caudate nucleus
83	0.028	-4	22	-10	32	L ACC/RCZa
	0.022	20	8	6		R putamen

<sup>1</sup> $P_{FDR} < 0.05$ ,  $k > 30$ , voxel size =  $2 \times 2 \times 2$  mm. ACC, anterior cingulate cortex; RCZa, anterior rostral cingulate zone; MPFC, medial prefrontal cortex; L, left; R, right. RCZa, RCZp, and CCZ are defined as by Fan et al. (2008).

**TABLE 5.**  
Brain Regions Involved in Empathy for Positive Emotions<sup>1</sup>

Voxel	ALE	x	y	z	Area	Label
128	0.014	-36	12	-4		L anterior insula
114	0.015	50	-46	18	13	R superior temporal gyrus
	0.011	54	-34	20	13	R superior temporal gyrus
60	0.015	-38	14	-26	38	L superior temporal gyrus
60	0.015	6	48	36	6	R MPFC
	0.015	8	48	36	8	R MPFC
60	0.014	50	2	40	6	R mid frontal gyrus
	0.014	50	2	42	6	R mid frontal gyrus
50	0.013	54	6	10	6	R mid frontal gyrus
46	0.010	-60	-32	40	44	L precentral gyrus
	0.010	-58	-26	40	40	L inferior parietal lobule
	0.009	-60	-40	38	1	L SI
43	0.012	34	28	-2	40	L inferior parietal lobule
41	0.011	46	-24	-2	47	L inferior frontal gyrus

<sup>1</sup> $P_{FDR} < 0.05$ ,  $k > 30$ , voxel size =  $2 \times 2 \times 2$  mm. SI, primary somatosensory cortex; MPFC, medial prefrontal cortex; L, left; R, right.



**Figure 2.** Empathetic pain as a test case to study the AIC-awareness relationship. **A:** Visual stimuli and task conditions used in empathetic pain paradigms (modified from Gu et al., 2010, 2013). **B:** After controlling for cognitive load, only AIC, and not ACC, showed increased activation for empathetic pain (modified from Gu et al., 2010). **C:** Cognition-emotion interaction effect in AIC (modified from Gu et al., 2013). **D:** AIC lesions, but not ACC lesions, are associated with diminished sensitivity to others' pain in the explicit empathy task (left, indexed by smaller  $d'$  based on signal detection theory) and lack of task-stimulus interference in the implicit empathy task (right, indexed by  $d'_{\text{painful}} - d'_{\text{nonpainful}}$ ; for details see Gu et al., 2012). AIC, anterior insular cortex; ACC, anterior cingulate cortex; NC, neurologically intact controls; BDC, brain-damaged controls; TP, task pain; TL, task laterality; TB, task body part. \*  $P < 0.05$ , \*\* $P < 0.01$ .

right AIC, but not the ACC, is also coupled with brain regions involved in task performance across different domains (Eckert et al., 2009).

We consider this evidence complementary to, rather than conflicting with, the finding of joint involvement of AIC and ACC. ACC does not seem to be a critical region

in generating awareness, yet it might receive input from AIC and convey the “feeling” information to other brain networks that serve voluntary control functions (Posner and Rothbart, 1998; Craig, 2009; Medford and Critchley, 2010; Valentini, 2010). This notion is supported by the functional connectivity between ACC and lateral prefrontal, primary, and supplementary motor areas during conflict processing (Fan et al., 2008). In other words, we borrow from the classical view that ACC serves as a limbic motor region and the AIC as a limbic sensory structure (Craig, 2009; Medford and Critchley, 2010).

### AIC integrates top-down and bottom-up information

Functional integration concerns the convergence (superadditive effect) of multiple mental operations. To demonstrate the involvement of any brain region in functional integration, at least two axioms need to be met: 1) corepresentation of each of the mental processes in that brain region and 2) an interaction between operations in the same region (Calvert, 2001; Gu et al., 2013). This definition is analogical to the idea of multisensory integration (MSI); in the presence of multiple sensory inputs, the firing rate of an MSI cell exceeds the sum of its responses to each input if processed separately (Roelfsema et al., 1997; Calvert, 2001). Investigating the integration of top-down and bottom-up information is crucial because it directly speaks to the general organizational principles of the brain (Dayan et al., 1995; Friston, 2002, 2012; Corbetta et al., 2008) and consciousness (Dehaene et al., 2006; Tononi and Koch, 2008; Dehaene and Changeux, 2011; Edlund et al., 2011). Top-down processes are often driven by task demand and largely voluntary; bottom-up processes, on the other hand, are mostly stimulus-driven and subject to voluntary control. In the framework of predictive coding and hierarchical inference, top-down, higher-level cortical activities try to predict or “explain away” the bottom-up sensory information conveyed by lower-level brain regions (Friston, 2002, 2010). The integration of bottom-up input and top-down recurrent information is considered essential for consciousness to occur (Tononi and Koch, 2008) and is likely to be subserved by long-distance projection neurons (Dehaene et al., 2006; Dehaene and Changeux, 2011).

We propose that AIC serves as a key node in such information integration process, based on findings of superadditive effects of task demand and stimulus valence in AIC (Fig. 2C, modified from Gu et al., 2013; for review see Sterzer and Kleinschmidt, 2010). Although much research has focused on the modulatory

effect of one mental process on another (Ochsner and Gross, 2005; Blair et al., 2007), fMRI evidence supporting functional integration is limited. One previous study suggests that dorsolateral PFC is involved in cognition–emotion integration (Gray et al., 2002); however, cognitive and emotional information were spatially and temporally segregated in the design, so one can speak only to the existence of distinct yet partially shared processing modules. In contrast, by simultaneously manipulating and top-down demand (e.g., laterality judgment TL and body-part judgment TB) and stimulus valence (e.g., pain, no pain), one can test a synergistic effect and introduce competition for neuroanatomical resources, an approach commonly used in sensory integration studies (Calvert, 2001). Behavioral data showed increased response time and error rates for painful compared with nonpainful stimuli under the difficult task TL relative to the easy task TB, indicating an interaction between stimulus valence (i.e., pain) and top-down influence (i.e., task demand). In parallel to behavioral findings, the activation of AIC and its related regions and networks such as somatosensory cortices showed corepresentation of stimulus valence and top-down effects and a superadditive interaction effect between cognitive load and stimulus valence, suggesting that information integration took place in these brain regions. Corepresentation of the cognitive evaluation and the stimulus valence of pain in AIC have been shown in previous studies (Salomons et al., 2004; Wager et al., 2004; Gu and Han, 2007a,b). Additionally, integration of stimulus predictability and subjective preference in right AIC is also reported for a juice delivery task (Berns et al., 2001).

The significance of these findings can be summarized as follows. First, The joint involvement of AIC and SI in integrating top-down and bottom-up information suggests that a possible “somatic marker” signal (Damasio, 1996) is activated when the processing of affective visual stimuli is guided by certain top-down requirements. Such signal might be subsequently conveyed to control regions such as ACC and prefrontal cortex for appropriate behavioral output. Second, information integration in AIC is supported by its anatomical (Mesulam and Mufson, 1982b; Saper, 2002) and intrinsic functional (Cauda et al., 2011; Deen et al., 2011; Touroutoglou et al., 2012; Chang et al., 2013) connectivity with a large scale network of sensorimotor, affective, and cognitive control regions. Third, the left AIC showed a more robust interaction effect (surviving in both ROI and whole-brain analyses) than the right AIC. We speculate that the left AIC might have advantageous access to structures involved in sensorimotor and cognitive control regions, which makes the integration easier compared

with the right AIC. Fourth, such synergy did not occur in ACC, which further suggests that AIC and ACC are functionally dissociable and singles out the significance of AIC in subjective awareness. These findings provide important, although not necessarily conclusive evidence, to help uncover the nature of high-level information integration and, potentially, awareness.

### AIC is necessary for emotional awareness

Finally, we demonstrate the necessity of AIC activity in emotional awareness by presenting evidence from neuropsychology studies. Although the insula has received increasing attention in the neuroimaging field, studies on the effects of focal insular lesions are still limited (for review see Jones et al., 2010). For instance, focal lesions in this region impair disgust perception (Calder et al., 2000). We examined both explicit and implicit empathetic pain perception in three patients with focal AIC lesions, in comparison with patients with focal ACC lesions and neurologically intact controls (Fig. 2D, modified from Gu et al., 2012). In the explicit task (Fig. 2D, left), AIC patients, but not ACC patients, displayed a striking impairment in sensitivity (measured by  $d'$ ) to others' pain when explicitly asked to evaluate pain, suggesting that AIC is *necessary* for explicit empathetic pain processing. In the implicit task of limb laterality judgment (Fig. 2D, right), control subjects showed a normal stimulus-task interference effect indexed by negative  $d'$  difference between painful and nonpainful stimuli (i.e., pain worsened judgment of laterality). However, AIC patients lacked such interference between stimulus valence and laterality judgment, indicating that the integration of stimulus-driven and top-down information was impaired in patients with AIC lesions and that AIC is necessary for bottom-up and top-down integration. Taken together, these findings demonstrate the necessity for AIC, but not ACC, in emotional awareness. Although AIC and ACC are usually considered as one system with AIC as the input sensory region and ACC as the output control region (Seeley et al., 2007; Craig, 2009; Jones et al., 2010), the finding that ACC is usually activated by but not necessary for empathetic pain perception suggests the existence of multiple control regions other than ACC and that AIC is the only critical input region.

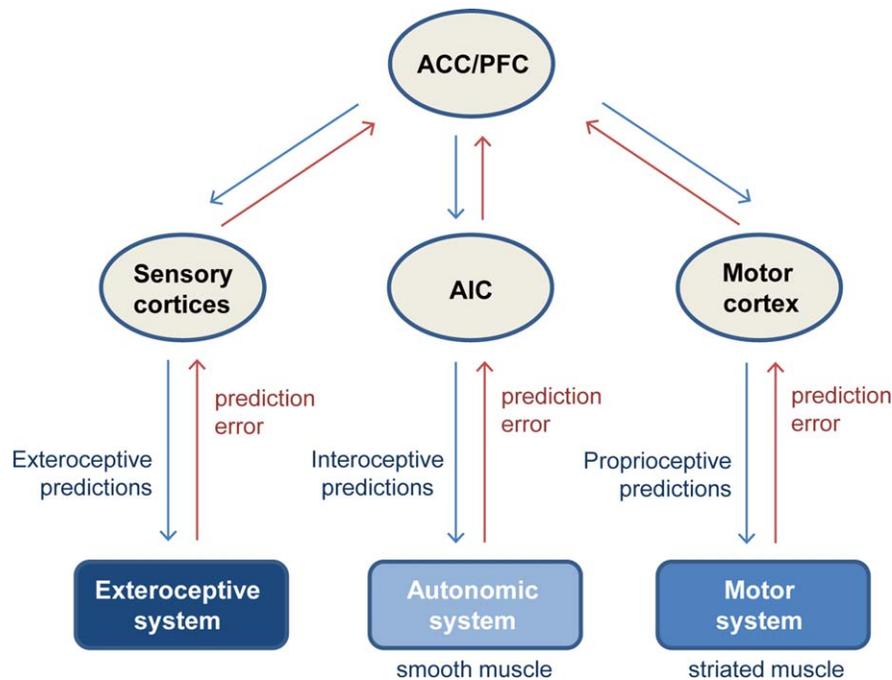
Three recent case studies specifically examined the effects of bilateral insular lesions on subjective awareness and reported intact interoceptive awareness (Khalsa et al., 2009) and self-awareness (Philippi et al., 2012; Damasio et al., 2013). The authors concluded that the insula is not necessary for awareness. Although we agree with the authors that emotional awareness is less likely to be subserved by one neural substrate

such as the insula and is more likely to be processed by distributed networks including low-level brainstem and thalamic nuclei, we next discuss possible sources of discrepancies in the findings among studies. First, although the insular lesions in the two patients “Roger” (Khalsa et al., 2009; Philippi et al., 2012) and “M” (Damasio et al., 2013) are bilateral, there are still residual tissues in the insula that might convey some interoceptive information (Craig, 2011). Second, the “core” self-awareness assessed by Damasio and colleagues (Philippi et al., 2012; Damasio et al., 2013) is based on self-recognition tasks, which are subserved by distributed neural networks also involving the frontal-temporal network (Keenan et al., 2000) and cortical midline structures (Zhu et al., 2007; Han and Northoff, 2009). Therefore, Roger and M might also be very likely to utilize their intact frontal regions in self-recognition tasks. Third, patient Roger did exhibit deficits in certain aspects of interoceptive awareness, as reported in supplemental materials by Khalsa and colleagues (2009). For instance, he was unable to detect heart rate change at low doses of isoproterenol infusion, his response lag was significantly longer than controls, and his interoceptive awareness was greatly worsened after anesthetic application (Khalsa et al., 2009). These findings are consistent with our findings on unilateral AIC lesions in that interoceptive and emotional awareness is impaired but not completely abolished in these patients.

### SUMMARY: A MODEL OF AIC AND EMOTIONAL AWARENESS

Based on the evidence described above, we propose that AIC plays a critical and necessary role in emotional awareness. Based on the hierarchical active inference scheme (Dayan et al., 1995; Friston, 2010) and several previous models on the insula (Craig, 2009; Singer et al., 2009; Seth et al., 2011) and awareness (Tononi and Koch, 2008), we consider a dual-process model (Fig. 3) in which AIC serves two major functions: 1) integrating bottom-up interoceptive prediction error signals with top-down predictions from high-level cortical areas and 2) providing descending interoceptive predictions to visceral systems that provide a point of reference for autonomic reflexes.

In the first (bottom-up) process, AIC functions as an interface between interoceptive input and top-down predictions from high-order cortical regions (i.e., PFC and ACC). This process is analogous to the role of sensory cortices such as visual and auditory areas in integrating bottom-up exteroceptive input with top-down signals (Fig. 3, left). This integration produces a signal representing



**Figure 3.** Hypothetical model of insula and awareness. In this hierarchical scheme, each lower-level structure receives descending predictions from and sends ascending prediction errors to higher-level regions. Anterior insular cortex (AIC) serves two major processes in this model (center): 1) integrating bottom-up interoceptive prediction errors with top-down predictions from high-order brain regions such as the anterior cingulate cortex (ACC) and prefrontal cortex (PFC), analogous to the role of sensory cortices (e.g., visual and auditory areas) in exteroceptive processing (left) and 2) sending descending predictions to the autonomic system via smooth muscles to provide a point of reference for autonomic reflexes, similar to the role of motor cortex in generating proprioceptive output via striated muscles (right).

the organism's current awareness state. We consider this signal to represent the current state of the organism that, on the one hand, is consistent with top-down predictions from higher-level representations of goals, actions, and attention (e.g., from ACC) and, on the other hand, best predicts future awareness states. This integration or synthesis of forward and backward signals is consistent with formulations of hierarchical inference in the brain and neuronal implementations based on predictive coding (see, e.g., Seth et al., 2011).

This notion is supported by empirical evidence of an integrative role of AIC, reviewed in previous sections, and is consistent with generative models of the brain and consciousness that suggest that the integration of bottom-up and top-down signals is important for subjective awareness (Friston, 2002, 2010; Tononi and Koch, 2008). According to a predictive coding account of the brain (Dayan et al., 1995; Friston, 2002, 2010), bottom-up stimulus-driven projections convey prediction errors, and top-down pathways convey active predictions. Therefore, functional integration in AIC also suggests a predictive coding role of AIC (Singer et al., 2009; Seth et al., 2011). One study specifically showed that AIC encodes both prediction of pain and pain prediction

error in the same task (Seymour et al., 2004), which directly supports the functional integration and predictive encoding account of AIC.

Recent developments in computational neuroscience support a role for AIC in encoding predictions and updating these predictions on the basis of bottom-up interoceptive prediction error. In line with the conceptual framework proposed by Singer and colleagues (2009), a recent empirical study shows that subjects use Bayesian rules to update their feelings and that (feeling) variance in prediction errors scale parametrically with AIC activation (Xiang et al., 2013). Another study showed that AIC is activated by not only prediction of risk but also the prediction error of risk (Preuschoff et al., 2008), which relates to unexpected uncertainty and state transition (Yu and Dayan, 2005). Sudden changes in reward contingencies and inquisitive policies also activate AIC (Li et al., 2006).

The second (top-down) process corresponds to the provision of descending predictions to visceral systems (i.e., via smooth muscles) that provide a point of reference for autonomic reflexes and sympathetic/parasympathetic outflow and for generating future awareness states. In other words, the AIC both responds to and

controls the internal milieu or literally “gut feelings.” The AIC is perfectly placed anatomically to do this; it is equipped with the anatomical and functional foundation to perform the very important task of inducing transitions in physiological states. As reviewed above, neurons in AIC innervate the viscera directly and indirectly, for example, through projections to the hypothalamic area via the amygdala. In short, AIC is able to cause changes in the physiological states of the body, in addition to perceiving changes from the body.

To illustrate the simplicity and potential power of this model, consider the analogous role of the AIC in controlling autonomic reflexes via smooth muscles and the motor cortex in controlling proprioceptive reflexes via striated muscles (Fig. 3, right). Recent predictive coding formulations of motor control consider descending corticospinal signals from motor cortex to provide predictions or set-points for classical reflex arcs in the spinal cord (Adams et al., 2013). In this view, descending predictions control behavior by enslaving peripheral reflexes. Our proposal here is exactly the same; however, the descending predictions are not of proprioceptive states but of interoceptive states, and the reflexes become autonomic in nature. Put simply, one might think of the insular cortex as a ventral extension of the sensorimotor strip that is concerned not with proprioception (and exteroception) but with interoception (Craig, 2002, 2009, 2011). This perspective has been developed by a number of authors (Allman et al., 2005; Seeley et al., 2006; Butti and Hof, 2010; Evrard et al., 2012) and nicely accommodates several observations reviewed above.

This model resolves the conceptual dialectic between the James-Lange theory and the Cannon-Bard formulations, in the sense that they are both right: bodily sensations both cause and are caused by central representations. This is a necessary consequence of hierarchical Bayesian inference and the recurrent exchange of neuronal signals implicit in predictive coding. The model also explains the findings suggesting that the insula serves a dual visceromotor and viscerosensory function.

- By analogy with the motor cortex, our model explains why the insular cortex possesses viscerotopic maps. Furthermore, like the motor cortex, the AIC is agranular. This is a remarkable exception to the laminar structure of the neocortex, which is shared only by the motor cortex, the ACC, and the AIC. This suggests a privileged role in the generation of descending predictions to peripheral systems.
- In predictive coding schemes, it is generally thought that top-down predictions originate in infragranular pyramidal cells. For example, in the motor cortex, descending predictions originate

from large pyramidal cells (e.g., Betz cells) in deep cortical layers. It is tempting to speculate that VENS of the AIC (which are located in layer V) play this role, as suggested by several investigators (Allman et al., 2005; Seeley et al., 2006; Butti and Hof, 2010; Evrard et al., 2012).

This perspective on the AIC as an integral part of hierarchical predictive coding in the brain explains the involvement of AIC across low-level autonomic and sensorimotor (Craig et al., 2000; Sterzer and Kleinschmidt, 2010; Fan et al., 2012) to high-level cognitive and social (Montague and Lohrenz, 2007; King-Casas et al., 2008; Bossaerts, 2010; Kirk et al., 2011) domains. This proposal does not preclude the participation of other brain regions in emotional awareness. On the contrary, AIC as well as other subregions of the insular cortex work closely coupled with other brain regions and networks (Cauda et al., 2011; Deen et al., 2011; Peltz et al., 2011) to translate different modalities of information effectively into subjective awareness. A posterior-to-anterior gradient of processing complexity exists within the insular cortex, with AIC representing the most complex and abstract end of this axis (Craig, 2009, 2010). AIC, in this sense, could be where the “sentient self” resides.

In summary, the proposed model extends previous models of AIC (Craig, 2009; Singer et al., 2009; Seth et al., 2011), although many details in the proposed AIC model remain unknown. For instance, what happens at the neuronal and molecular levels during the actual information integration process? How does information flow among AIC, ACC, and many other closely related structures? How do deficits in these processes manifest in disease? Finer-grained quantitative investigations and combination of neuroimaging, lesion, stimulation, biochemical methods, and theoretical neurobiology are needed to answer these questions, to advance our understanding of functions of the insular cortex and human emotional awareness.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## ROLE OF AUTHORS

Drafting of the manuscript: XG. Meta-analysis: XG, JF. Design of the study: XG, JF, PRH. Critical revision of the manuscript for important intellectual content: PRH, KJF, JF.

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