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REVIEW

Anterior insula activations in perceptual paradigms: often observed but barely understood

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Abstract Anterior insular cortex is among the non-sensory brain regions most commonly found activated in functional brain imaging studies on visual and auditory perception. However, most of these studies do not explicitly address the functional role of this specific brain region in perception, but rather report its activation as a by-product. Here, we attempt to characterize the involvement of anterior insular cortex in various perceptual paradigms, including studies of visual awareness, perceptual decision making, cross-modal sensory processes and the role of spontaneous neural activity fluctuations in perception. We conclude that anterior insular cortex may be associated with perception in that it underpins heightened alertness of either stimulus- or task-driven origin, or both. Such a mechanism could integrate endogenous and exogenous functional demands under the joint criterion of whether they challenge an individual's homeostasis.

Keywords Visual perception · Auditory perception · Anterior insular cortex · Functional magnetic resonance imaging

Introduction and aims

Originating from reports on intraoperative recordings by Penfield et al. in the 1950s (Penfield and Faulk 1955), anterior insular cortex (AIC) has long been thought of as a visceral sensory region (Saper 2002). Consistent with the James–Lange theory of emotion and the somatic marker hypothesis (Damasio 2003), it was suggested that through the representations of bodily reactions, e.g., in response to emotional stimuli, AIC could play a central role in mediating interoceptive awareness and the subjective experience of feelings (Craig 2002). In recent years, this notion has been substantiated and refined by evidence from a number of studies using functional neuroimaging, especially functional magnetic resonance imaging (fMRI) (Critchley 2005; Craig 2009). Functional magnetic resonance imaging (fMRI) allows nearly simultaneous measurements of neural activity changes across the whole brain, and many studies with this technique have revealed that AIC activations are not limited to the processing of emotional or affective information. Activations in the AIC, along with anterior cingulate cortex (ACC), are in fact among the most commonly reported foci in cognitive tasks, including those probing processes underlying perception and awareness. The widespread involvement of AIC in perceptual processes has led to the suggestion that the role of AIC might not be limited to interoception and subjective feelings, but that it could be generally involved in mediating awareness (Craig 2009).

The aim of this study was to review the literature with respect to the role of AIC in visual and auditory perception. Perception here refers to the process of registering sensory stimuli as a meaningful experience. Since the evidence of the AIC playing a general role in perception is derived in majority from functional neuroimaging studies, we will

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focus on this literature. While the AIC is a region that is commonly found to be activated in studies of perception in the visual and other modalities, it should be noted that most of these studies did not actually target AIC function. Rather, AIC activation is usually found more or less incidentally as part of a larger network comprising the dorsal ACC, lateral prefrontal cortex and parietal regions. Interpretations of such findings are mostly post hoc, and there is even a certain degree of circularity, as the interpretation of insula activations often refers to other studies that also found insula activity as a by-product, or at least without a strong a priori hypothesis concerning this region. AIC activation is usually part of a response in a distributed set of other brain regions, which makes interpretation of its role in perception even more challenging. Again, hardly any neuroimaging study attempted to define the specific function of AIC in perception in contradistinction to that of other frontal and parietal regions.

Even though our review will in most parts also be confined to a post hoc interpretation of many more or less accidental findings, we nevertheless believe that the role of the AIC in perception can be characterized to some extent from a synopsis of the existing literature. The purpose of our review is to provide a framework for testable hypotheses regarding this role, which might serve as a basis for future dedicated investigations of this brain region. Most importantly, we will pursue the question of specificity: can a distinct functional process within perception be tied to AIC, and only to AIC function, or does AIC activity in allegedly perceptual paradigms reflect its participation in a more general function that is common to a wide variety of cognitive processes? Within the field of perception, we will focus on research areas that have discussed AIC as a key player and have assigned it a specific role. These include studies of visual awareness, perceptual decision making and cross-modal sensory processes. Finally, we will highlight recent findings from the study of spontaneous fluctuations of neural activity, which may help to provide a more complete understanding of the insula's role in perception. We will not review research on emotional processes or on music and time perception as these topics are covered extensively by other articles in this issue, but our analysis will touch on issues related to attention (see also the article by Nelson et al. (2010), in this issue).

Visual awareness

We use the term awareness in the sense of perceptual awareness, which indicates the ability of an observer to report either the presence of a stimulus or its identity (Rees 2007). Several studies have shown that awareness of visual stimuli, or of certain aspects of visual stimuli, is associated with fMRI activations in a frontoparietal network comprising AIC, dorsal anterior cingulate cortex (ACC), lateral prefrontal cortex (mostly middle frontal gyrus) and parietal cortex (mostly intraparietal sulcus) (Rees 2007). For example, a combined fMRI and EEG study investigated the neural processing of visible words compared to words rendered invisible by a combination of forward and backward masking (Dehaene et al. 2001). Greater activations during processing of visible words were found in bilateral AIC and other frontoparietal regions including the dorsal ACC, left inferior frontal cortex and left intraparietal sulcus. A strong effect of word visibility was also found in the visual word form area, a region in the lateral fusiform gyrus that responds preferentially to the visual presentation of written words (Cohen et al. 2000). It was concluded that frontoparietal regions, including the AIC, may play a role in awareness by means of a top–down amplification of signals in the visual cortex. It is important to note that this study used a stimulus manipulation to modulate visibility, which leaves the possibility that any difference in brain responses expresses differences in visual stimulation. An elegant approach to avoid this problem is to use near-threshold settings where a certain property of a single given stimulus will reach awareness on some trials, but not on others. Studying fMRI responses to visual flicker, one study presented flickering visual stimuli at the threshold of the visual system's ability to differentiate between two sequential stimuli (flicker-fusion threshold), resulting in perception of the two stimuli as either flickering or fused (Carmel et al. 2006). Perception of flicker in this stimulus was associated with activations in the right AIC, middle frontal gyrus and intraparietal sulcus. The authors concluded that these areas may thus be involved in the awareness of temporal properties of the visual environment. As in many studies on neural correlates of consciousness, however, it remains difficult to discern on the basis of fMRI signals whether these activations are cause or consequence of a specific percept, in this case perceiving flicker. It could be that a critical amount of activity in these areas, for instance related to alertness or attentiveness, is necessary for perceiving a flicker stimulus at threshold. Alternatively, insular and frontoparietal activations could reflect a bottom-up signal related to the greater salience once the stimulus is perceived to flicker.

Do the findings of greater insular activity during awareness versus unawareness of visual stimuli reflect differences in stimulus visibility? Researchers have attempted to answer this question by parametrically modulating stimulus visibility. Deary et al. (2004) varied the presentation duration of a target stimulus that was followed by a mask stimulus. Participants performed a forced-choice discrimination task on the target stimuli. As a consequence, task difficulty increased with decreasing inspection times.

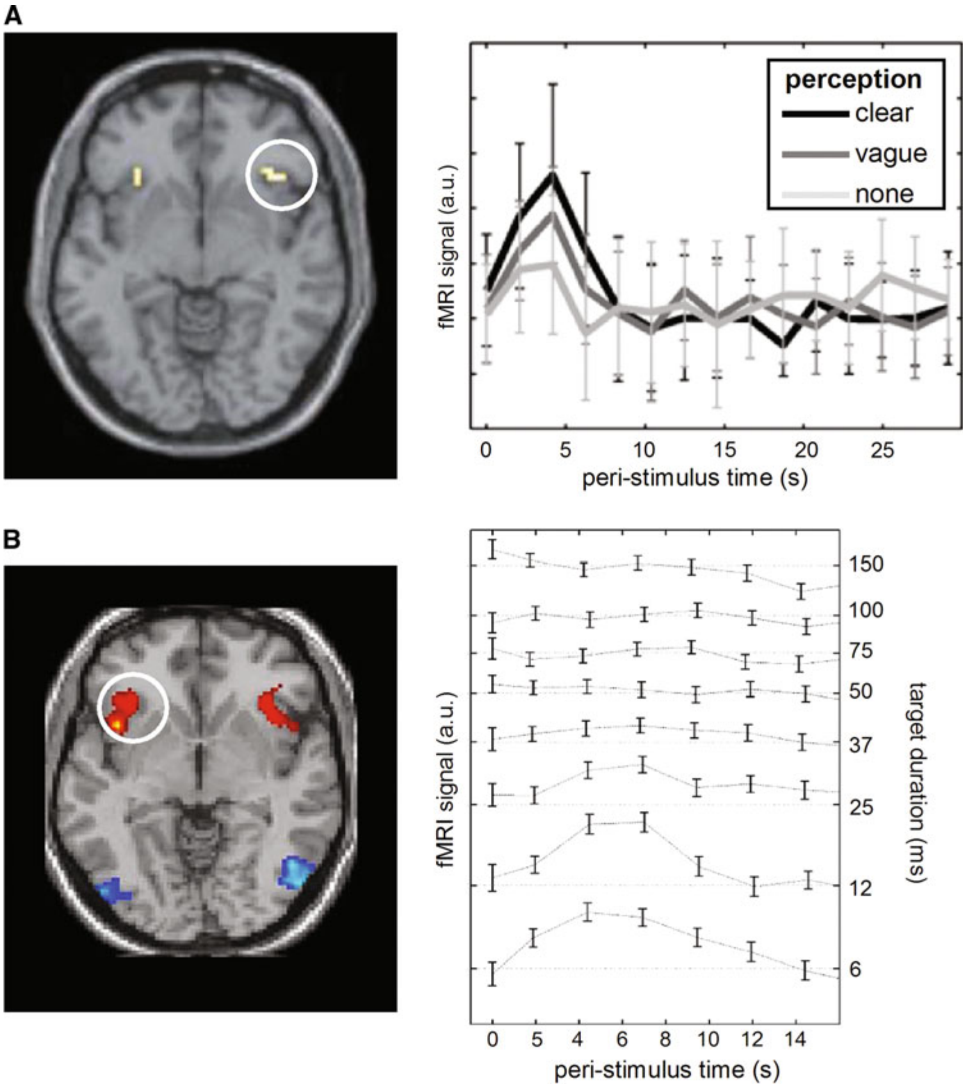

Fig. 1 Stimulus- and task-dependent modulation of anterior insular cortex activity. Examples are from two studies that used a similar manipulation of stimulus visibility, but found opposite response profiles of anterior insular cortex. **a** Stimulus visibility was manipulated by varying presentation duration in a backward-masking paradigm. Data were analyzed as a function of participants' subjective ratings of stimulus visibility. Responses in bilateral anterior insula correlated positively with subjective visibility ratings (Christensen et al. 2006). **b** Stimulus visibility was again manipulated in a backward-masking paradigm by varying presentation duration as indicated on the *y*-axis of the *right panel*. In this study, participants had to perform a forced-choice task on the target stimuli, which was increasingly difficult with shorter presentation durations and thus decreasing visibility. Contrary to the study by Christensen et al. (2006), bilateral anterior insula activity now correlated negatively with stimulus visibility (Deary et al. 2004)

When analyzing fMRI responses as a function of inspection time, a robust negative correlation was found in AIC and dorsal ACC. That is, insular responses where greatest at very short inspections times (6 ms), when performance was at chance level because targets were invisible. Interestingly, the apparently opposite finding was obtained in a study where stimulus visibility was again modulated by presentation duration in a backward-masking paradigm (Christensen et al. 2006). In this study, however, the task was not to discriminate between two stimuli, but just to rate stimulus clarity. The subjectively perceived stimulus clarity, which was low for short presentations and high for long presentations, correlated positively with the fMRI signal in a network comprising the AIC and frontal operculum bilaterally, among other inferior frontal, parietal regions and the basal ganglia. That is, depending on task demands, a similar stimulus manipulation (presentation duration with backward masking), which had a similar effect on perception (reduced visibility for shorter presentation durations), was associated with exactly the opposite response profile in AIC (Fig. 1): Responses in the AIC correlated negatively with stimulus visibility during a forced-choice discrimination task (Deary et al. 2004) and positively during a subjective visibility rating task (Christensen et al. 2006). An even earlier study manipulated visibility by slowly increasing and then degrading stimulus contrast around threshold values and compared brain activity as a function of whether the same stimulus contrast induced awareness or not (Kleinschmidt et al. 2002). While the absence of evidence can in principle always relate to a lack of sensitivity of a given stimulus paradigm to evoke activations in a particular brain region, it is still noteworthy that this approach did not yield insular activations in correlation with stimulus awareness. Interestingly, the task requirements in that study were not tied to awareness, but to changes in awareness, either way, with emergence or loss of a percept being reported by the participants. This raises the possibility of AIC activity responding to perceptual factors only when they are relevant to action.

Together, these studies suggest that AIC activations reflect task demands to a greater degree than awareness of a target stimulus, that is, conscious perception of this stimulus. In other words, the role of the AIC in perception seems to be more tightly coupled to the perceptual task than to awareness of a stimulus per se. This notion is supported by a study investigating blindsight in a patient with a complete unilateral lesion of primary visual cortex. In this patient, engagement in a visual discrimination task was associated with right AIC activation that was particularly strong in the unaware mode, i.e., when stimuli were presented in the blind hemifield (Sahraie et al. 1997). This finding speaks of the possibility that AIC activation may reflect task difficulty rather than awareness per se (see also review on time perception by Kosillo and Smith (2010), in this issue). Such a view on the insula's role in perception may help to explain why several more studies than the one mentioned above (Kleinschmidt et al. 2002) that compared awareness and unawareness of visual events failed to observe AIC activations. For example, in the attentional blink paradigm, i.e., the failure to detect the second of two targets that rapidly succeed each other and are embedded into a stream of distracter stimuli, hits are associated with greater activity in the frontal and parietal areas, but not in insular cortex (Marois et al. 2000, 2004). Similarly, no insular activations were observed during the detection of changes in visual stimulation in a change-blindness paradigm, whereas dorsolateral prefrontal cortex and parietal cortex showed significant activations in association with change detection (Beck et al. 2001). Of course, the caveats of negative findings again apply here. But if AIC involvement is not directly related to visual awareness, the absence of insular activations in these studies might be due to the fact that the related task demands do not differentially recruit the AIC.

But what then is the role of the AIC in the awareness of sensory stimuli? Further insight into this question comes from studies that probed neural responses to sensory stimuli in the absence of a specific task. Downar et al. (2000) presented simple visual, auditory and tactile stimuli simultaneously and iteratively with occasional stimulus changes in one of the three modalities. They found right AIC as part of a frontoparietal network comprising the dorsal ACC, lateral inferior frontal cortex and temporoparietal junction. This set of regions was activated during stimulus changes irrespective of the sensory modality. As participants did not perform any task, these activations were interpreted as reflecting a multimodal network for involuntary attention and thus for awareness of sensory events (see Corbetta and Shulman 2002). Along similar lines, a recent study used fMRI to identify brain regions that are commonly activated by four different sensorimotor tasks, which shared neither sensory input nor motor output (Ivanoff et al. 2009). AIC and lateral prefrontal cortex were commonly activated across all four tasks and were thus suggested as candidate neural substrates for a central hub of information processing across sensory modalities. Of course, these approaches, while doubtlessly informative, cannot ultimately clarify to what extent such an amodal network's activity is essential, supportive or collateral. Finally, AIC activation is also observed in association with perceptual events that occur in the absence of changes in sensory stimulation, e.g., during bistable perception. One study reported covariation of right AIC, inferior frontal and inferior parietal activity with visual cortex activity during binocular rivalry, suggesting that these regions may mediate awareness of activity changes in sensory brain regions that are associated with spontaneous changes in perception (Lumer and Rees 1999). Similarly, an increase in fMRI signal in the AIC was observed after perceptual switches during bistable apparent motion perception, along with activations in the visual motion complex V5/MT and the supplementary motor area (Muller et al. 2005).

To summarize the findings from studies that have implicated the AIC in the awareness of sensory information, we shall first note that none of the studies reviewed here support a unique and specific role of the AIC in awareness. In functional imaging studies, the AIC is almost always identified as part of a larger network of jointly activated frontal and parietal brain regions. Further, it seems that stimulus salience drives responses in the AIC. Salience here is used in its most general sense as indicating that a stimulus is particularly noticeable or important. Visible stimuli are usually more salient compared to invisible ones and are thus often found to be associated with AIC activations. Likewise, changes in sensory stimulation are salient events, especially if they occur rarely. However, insula responses to sensory events also seem to be closely linked to perceptual task demands and effort in particular. Effort as used here refers to the degree to which mental or cognitive resources are mobilized for completing a given task. If the task is to discriminate between two types of stimuli, AIC activity increases with decreasing stimulus visibility, that is, the less salient the stimulus is, the more the effort needed to detect the stimulus increases. How can these seemingly opposing mechanisms be reconciled? Possibly, AIC activity does not express perceptual salience per se, but rather the recruitment of processing resources when faced with a given sensory event, whatever the source of that recruitment, bottom–up or top–down. Salient events are usually assigned processing resources, which are conceptualized as exogenous or bottom-up allocation of attention. On the other hand, if this is required by the task at hand, processing resources become more necessary as the stimulus is less salient. Accordingly, AIC has been implicated in the effort required by a perceptual task in the field of perceptual decision making, which we will turn to next.

Perceptual decision making

Perceptual decision making is defined as the act of choosing one option or course of action from a set of alternatives on the basis of available sensory evidence (Heekeren et al. 2008). A typical experimental approach for investigating the mechanisms of perceptual decision making is to have study participants perform sensory discrimination tasks, with the sensory input being more or less degraded. In the visual domain, for example, a direction-of-motion discrimination task in which participants have to indicate the net motion of a noisy field of moving dots is a commonly used paradigm for the investigation of perceptual decision making (reviewed in Gold and Shadlen 2007). While there is converging evidence for the notion that activity in sensory brain areas closely reflects the amount of available sensory evidence in favor of a given decision, the role of higher-order non-sensory regions in the decision process remains controversial (Heekeren et al. 2008). A number of fMRI studies have suggested that the AIC plays an important role in the perceptual decision process. For example, it has been shown in a series of studies that trial-by-trial fluctuations in the left AIC correlate with decisions about fearful and non-fearful faces (Pessoa and Padmala 2005, 2007; Thielscher and Pessoa 2007). Most relevant in our current context, Thielscher and Pessoa (2007) used a graded series of morphed emotional faces and asked participants to indicate the faces' emotional expression. They observed an inverted U-shaped correlation between reaction times and BOLD responses in the AIC and the ACC, using reaction time as an index of decision processes. In other words, longer reaction times, which indicate a more difficult perceptual decision, were associated with greater AIC and dorsal ACC activations. Along similar lines, difficulty of perceptual decisions was modulated by varying noise levels in an auditory discrimination task (Binder et al. 2004). While accuracy correlated positively with activity in the auditory cortex, reaction time as a marker of task difficulty correlated positively with the BOLD signal in AIC. Interestingly, a nearby region at the border of AIC and frontal operculum showed a negative correlation with accuracy, which can be seen as another index of task difficulty. Accordingly, AIC and ACC activation increases as a function of acoustic stimulus complexity during speech comprehension, most likely reflecting task difficulty (Giraud et al. 2004). Grinband et al. (2006) manipulated decision uncertainty independently of the stimulus evidence in a task with a variable categorization boundary. Uncertainty correlated with activity in the AIC as part of a larger network comprising the medial frontal gyrus, ventral striatum and dorsomedial thalamus. Finally, EEG components that are related to difficulty in perceptual decision making correlate with fMRI signals in the AIC, the ACC and dorsolateral prefrontal cortex (Philiastides and Sajda 2007). The finding of greater AIC activations with increasing task difficulty in perceptual decision-making studies (Binder et al. 2004; Grinband et al. 2006; Philiastides and Sajda 2007; Thielscher and Pessoa 2007) is reminiscent of the aforementioned study by Deary et al. (2004). Although the latter did not explicitly conceptualize their experiment in the framework of perceptual decision making, they in fact also varied the difficulty of a perceptual decision task. AIC activity related to task difficulty could hence reflect the degree of cognitive effort that is required for a task. The notion of cognitive effort can account for AIC recruitment in a number of perceptual paradigms (e.g., those that manipulate the presence of noise in a stimulus, presentation duration or categorization uncertainty), but also in non-perceptual paradigms. For example, the feeling of knowing a word before actually recalling it has been associated with a region at the border of AIC and inferior frontal gyrus, where fMRI responses parametrically increase with greater feeling of knowing (Kikyo et al. 2002). The involvement of AIC and inferior frontal gyrus in this paradigm could reflect increased cognitive effort when striving for the recall of a word that one strongly feels one knows. In the context of perceptual decision making, the role of the AIC might thus be to translate cognitive effort into increased sensory alertness to improve perceptual performance.

Another line of research into the neural mechanisms of perceptual decision making has associated AIC activity with the moment at which the perceptual decision is made, rather than task difficulty. One study (Ploran et al. 2007) measured brain activation with fMRI while participants watched a screen on which an image was slowly being revealed. While activity in visual areas increased as a function of the amount of sensory information available, there was a sudden increase in activity in the AIC and the dorsal ACC at the moment of recognition, which here refers to being able to identify a visual object stimulus (e.g., butterfly). This finding was interpreted as reflecting cognitive processes related to stimulus recognition rather than those linked to the decision process itself. A different conclusion was reached by another study (Ho et al. 2009), in which stimulus information gradually increased either quickly (easy trials) or slowly (hard trials). fMRI responses were modeled on the basis of a linear ballistic accumulator model, which predicts that regions involved in the perceptual decision process will show smaller but earlier responses in easy trials compared to hard trials. The authors identified the AIC as the only brain region to match this response profile irrespective of the response mode, that is, independently of whether responses were made with eye movements or button presses. Especially, the observation that the rise in BOLD signal occurred earlier during easy trials was taken as evidence that this region is not simply recruited by general arousal or by the tonic maintenance of attention. One could argue, however, that an earlier activation is not necessarily related to the perceptual decision process itself, but could just as well reflect the perceived stimulus salience at the moment of recognition, in line with the above-mentioned study by Ploran et al. (2007). Together, findings from perceptual decision making thus again suggest that both perceived stimulus salience, i.e., 'pop-out' in space or time, and task difficulty recruit the AIC.

Cross-modal interactions

While most studies reviewed above were concerned with visual perception, we have seen that the AIC may be involved in perceptual processes in different sensory modalities (e.g., Manes et al. 1999; Downar et al. 2000). It was proposed, however, that the AIC may not only play a role in perception independently of the sensory modality, but especially in cross-modal interactions by mediating communication and exchange of information between unisensory areas (Calvert 2001; Amedi et al. 2005). The insula is strongly connected to various sensory areas and is hence a plausible candidate to accomplish this function (Mesulam and Mufson 1982; Mufson and Mesulam 1982). In the following, we discuss neuroimaging studies that suggest an involvement of insular cortex, especially AIC, in cross-modal visual–tactile or visual–auditory interactions.

Cross-modal interactions in central sensory processing have been studied in various ways. Studies that implicated the insular cortex in cross-modal processing have used cross-modal matching tasks, stimuli with a mismatch between modalities or cross-modal binding phenomena. In cross-modal matching tasks, participants have to match objects using two sensory domains independently, e.g., by either touching objects or looking at them. The performance of such visuo-tactile matching tasks is associated with insular activations, but these activations were located in the mid-posterior insula rather than AIC (Hadjikhani and Roland 1998; Banati et al. 2000). In contrast, mismatch between sensory modalities seems to consistently recruit the AIC. In one PET study, for example, visual and auditory stimuli were presented either synchronously or asynchronously with varying delays (Bushara et al. 2001). Comparing asynchronous and synchronous conditions, this study delineated a large-scale network comprising AIC as well as prefrontal and posterior parietal regions during asynchronous stimulation. Interestingly, increasing task demand (i.e., decreasing intermodal delay) correlated with activity in the right AIC only. It was concluded that the AIC is critically involved in mediating cross-modal interactions but without controlling for the generic effect from effort induced by mismatch. In a related study, where cross-modal integration of speech was investigated, auditory and visual speech stimuli were presented synchronously or asynchronously (Miller and D'Esposito 2005). Activity in a broad network of regions including the AIC, the superior colliculus and intraparietal sulcus was sensitive to spatiotemporal correspondence. Similar to the study by Bushara et al. (2001), these regions showed greater responses during asynchronous stimulus presentation. The AIC is also activated during other types of auditory–visual mismatch, e.g., when the consonants in auditory speech stimuli do not match with those shown in visual stimuli as in the so-called McGurk effect (McGurk and MacDonald 1976; Benoit et al. 2009).

Finally, the AIC has also been implicated in cross-modal binding. Cross-modal binding refers to situations where information from one sensory modality changes the way a stimulus in another modality is perceived. A phenomenon that has been used to investigate cross-modal binding is the effect of sound on motion perception. When two identical visual objects move toward each other, overlap and then continue their original motion, they are perceived either as bypassing each other or as colliding and reversing their direction of motion. Introducing a sharp sound at the time of overlap biases observers to perceiving a collision (Sekuler et al. 1997). In an fMRI study, identical auditory–visual stimuli were presented in all trials, but in some trials they were perceived to be bound together and in others they were perceived as unbound unimodal events (Bushara et al. 2003). Cross-modal binding was associated with activations in the AIC bilaterally, among other regions in dorsolateral prefrontal cortex, superior parietal cortex and the superior colliculi. A different finding was reported by the above-mentioned recent study that used the McGurk effect to study cross-modal binding (Benoit et al. 2009). While mismatching auditory–visual input was associated with increased fMRI signal in the AIC, this signal correlated negatively across participants with the degree of McGurk fusion, i.e., the proportion of trials where auditory perception was overruled by visual information. Thus, AIC activity in this study less likely reflected cross-modal binding, but rather the perceived mismatch between modalities which in turn can be considered an important contribution to the salience of a given trial or the effort in performing a task.

With the exception of one study that identified right AIC as the single region that correlated with task demands (Bushara et al. 2001), most studies reported cross-modal effects in the AIC as part of a large-scale network of regions. The exact role of local AIC-based processes in multimodal sensory perception thus remains to be determined. The fact that insular cortex is highly connected to all sensory cortices certainly speaks of the notion that it plays a key role in assigning processing resources to those sensory stimuli that are currently most relevant according to stimulus- or task-related criteria. Again, AIC activations in cross-modal studies can be attributed to task demands (Bushara et al. 2001) or to perceived stimulus salience, which may be the key factor in mismatch-related responses (Bushara et al. 2001; Benoit et al. 2009). But why should the AIC show stronger activations in cross-modal binding as reported by Bushara et al. (2003)? It is conceivable that the degree of activation in AIC and other related regions determines the amount of processing resources that are assigned to the two stimuli, and that the likelihood of perceiving them as bound together increases if they are both assigned more processing resources.

Spontaneous fluctuations of AIC activity

As in the aforementioned study (Bushara et al. 2003), a question of causality arises in many studies that report activations in the AIC in association with perceptual events: are insular activations the cause or the consequence of conscious perception? For example, does a stimulus reach awareness because activity in the AIC reaches a critical level, or is AIC recruited in response to a stimulus reaching awareness? The best evidence for causality that correlative measures as functional neuroimaging can establish comes from demonstrating temporal precedence. In other words, if neural activity at a given point in time is predictive of future neural activity elsewhere, or of perceptual performance, this suggests a causal role of activity at this given site. Exploiting such relationships between temporal activity profiles across different areas of the brain is at the heart of the family of so-called effective connectivity analyses, as for instance dynamic causal modeling (Friston et al. 2003) or Granger causality (Goebel et al. 2003). Two aspects of functional brain anatomy plague these analyses: first, brain areas are predominantly connected by bidirectional pathways anatomically; and second, local activity may be functionally related both to causes and consequences of a given perceptual process. In conjunction with topographic variations in signal-to-noise ratio of activations and the temporal dispersion of hemodynamic relative to neural signals, this makes a fine-grained analysis of temporal patterns of brain activations very difficult. A more direct and simple chronometric approach, albeit successful in some instances, cannot fully avoid these problems either and is only valid if phrased as a region-by-condition interaction (Sterzer and Kleinschmidt 2007).

More recently, however, the interest in temporal relationships has been rekindled by studies that have evaluated the effects of spontaneous variations of ongoing activity on brain activations and behavioral outcomes that are elicited by subsequent stimuli. Widely used analytical methods leave this variance from ongoing activity fluctuations unaccounted for, but there are several reasons for reconsidering this approach (Fox and Raichle 2007). Firstly, ongoing activity is quantitatively vastly superior to any stimulus- or task-driven increment. Secondly, it displays considerable fluctuations that are easily in and above the range of task-related signal modulations. Thirdly, ongoing activity is organized into coherent networks that are well known from explicit paradigm-based studies of brain function (Smith et al. 2009). Finally, trial-by-trial variations in ongoing activity have been demonstrated to impact on and hence partially account for perceptual and behavioral variability in a complex, non-linear fashion (Boly et al. 2007; Fox et al. 2007; Hesselmann et al. 2008a, b; Sadaghiani et al. 2009).

The insula has a very interesting strategic position within these so-called resting state networks, i.e., sets of regions that display correlated signal modulations in the absence of an explicit task paradigm. Firstly, its association with other brain regions shows an anterior–posterior subdivision (Taylor et al. 2009). Secondly, the anterior insula has been suggested as part of several differently labeled resting state networks (Dosenbach et al. 2007; Seeley et al. 2007; Vincent et al. 2008). Of note, many of these studies rely on using a seed region. The whole brain analysis then searches for other regions showing a similar simultaneous time course. Such analyses are highly sensitive to the precise anatomical location of the seed region, and variability in the results using seed regions in the anterior insula hence suggests a hub function of the anterior insula reflecting a widespread connectivity with fine-grained local variations. Functional evidence for a hub role of the anterior insula in orchestrating behavior across different networks, including a dorsal frontoparietal network implicated in executive functions and the so-called ‘default-mode’ network, comes from combined task and resting state experiments (Sridharan et al. 2008; Eckert et al. 2009). Again, the anterior insula was tightly tied to anterior cingulate in resting state and in stimulus-related experiments sensitive to salience of sensory events across modalities and also to task demands.

We have recently studied the effect of activity variations in this network, which additionally includes thalamic regions, on perceptual performance by asking subjects to

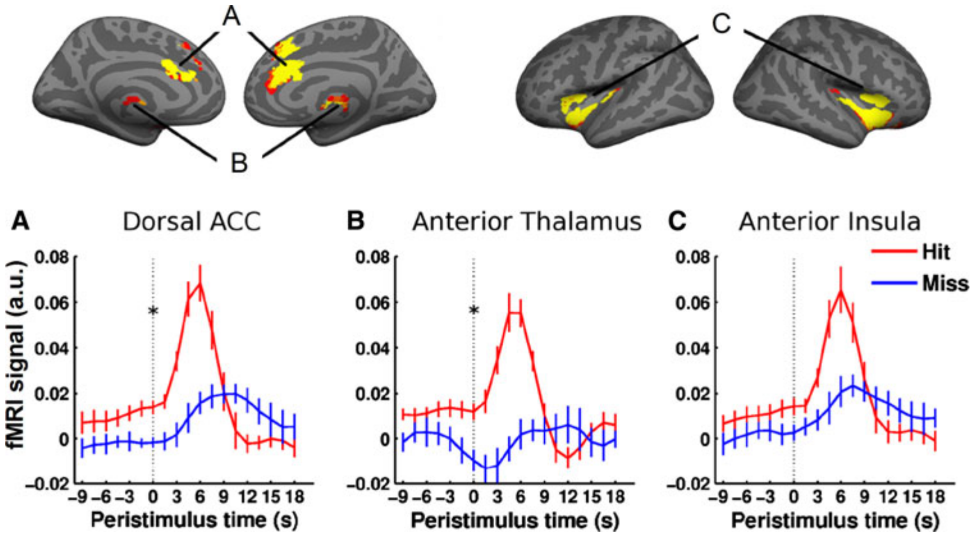

Fig. 2 Spontaneous activity fluctuations in anterior insular cortex influence auditory perception. Higher ongoing activity in the dorsal anterior cingulate cortex (**a**), anterior thalamus (**b**), and anterior insular cortex (**c**) prior to the presentation of near-threshold auditory stimuli is predictive of detection performance in the upcoming trial (Sadaghiani et al. 2009)

detect during (noisy) scanning the sparse and unpredictable occurrence of near-threshold acoustic stimuli (Fig. 2). We found that higher ongoing activity in this network prior to stimulation was predictive of detection in the upcoming trial (Sadaghiani et al. 2009). This task is far from requiring great executive control or selective attention and our paradigm resembles those that have been used in experiments on vigilance fluctuations (Makeig and Inlow 1993). In accord with explicit studies using stimulation paradigms (Sturm et al. 2004), we have hence proposed that this network mediates tonic alertness. This interpretation is compatible with other accounts that have emphasized the maintenance of a task set (Dosenbach et al. 2006, 2007), but appeals to an ecologically more intuitive and basic cognitive function. Indeed, we believe that the tonic and phasic aspects of alertness are sufficient to reconcile the entirety of functional neuroimaging findings on the relationship between insula with the perception that we have discussed above. More challenging task requirements will raise alertness as will the greater salience of a sensory event propagated to higher-order areas. The central role of alertness, which implies the readiness to respond to a stimulus and to (re-)act accordingly, for the integration of perception and action is in line with the integrative structural and functional hub role of the insula that a vast number of studies have established (Dosenbach et al. 2006; Sporns et al. 2007; Sridharan et al. 2008; Eckert et al. 2009).

Discussion and conclusions

We have attempted to illustrate that AIC is involved in a multitude of perceptual tasks. Although evidence is most abundant for the visual domain, this cortical region seems to be involved in perception in all sensory modalities. As mentioned in our introduction, it is important to note that most of the studies in this field have not addressed the role of AIC in perception explicitly. There is thus little experimental evidence from dedicated experiments that would help to directly disambiguate the potential role of the AIC in various aspects of perception and maybe also provide a more fine-grained anatomical mapping of such functions within this region. In reviewing the existing evidence, we have tried to integrate in a post hoc fashion information from a number of studies that have observed activations in the AIC, many of them more or less accidentally. To nevertheless arrive at a reasonable interpretation of AIC function in perception, it seems helpful to ask three central questions: (1) What is common to all perceptual tasks that are associated with responses in the AIC? (2) Are there distinct patterns of co-activation with other brain regions? (3) What is the possible connection with the AIC's role in other domains of cognitive, emotional or autonomic processing?

What is common to all perceptual tasks associated with AIC activations? At first sight, there seem to be various different aspects of perception that recruit AIC. Many of the findings reviewed above suggest that the AIC responds to the perceived salience of sensory events. Salience can be a function of physical stimulus properties (e.g., contrast, duration) and is often determined relative to other stimuli, e.g., by distinctive characteristics that differentiate a stimulus from neighboring stimuli both in space and time. Accordingly, AIC activations are observed in association with stimulus visibility per se (Dehaene et al. 2001; Christensen et al. 2006), but also at the moment of recognition of a stimulus in noise (Ploran et al. 2007; Ho et al. 2009). Salience refers also to sensory events that stand out as 'oddballs' because they are different from most other stimuli (Downar et al. 2000), or because they are different from learned expectations, as in the case of a mismatch between auditory and visual stimuli (Bushara et al. 2001; Benoit et al. 2009). Of note, perceived salience can also refer to perceptual events that occur in the absence of changes in sensory stimulation, such as spontaneous perceptual changes during bistable perception (Lumer and Rees 1999; Muller et al. 2005; Sterzer et al. 2009). As discussed above, stimulus salience is not the only determinant of AIC activation, as task demands seem to strongly recruit the AIC (Binder et al. 2004; Deary et al. 2004; Grinband et al. 2006; Philiastides and Sajda 2007; Thielscher and Pessoa 2007). Finally, AIC activations are also observed in association with one of two possible percepts in situations of perceptual ambiguity, where the salience of one over the other percept is not immediately obvious (Bushara et al. 2003; Carmel et al. 2006). A possible explanation in these cases could be that for one percept to occur, more processing resources are required than for the other and that these resources are made available through activation of a neural circuit that includes the AIC. Thus, the picture emerges that the AIC is activated whenever the sensory input poses a challenge. This challenge can take various forms: information that stands out because of particular stimulus features and therefore captures processing resources; information that is novel or unusual and therefore calls for the deployment of additional processing resources; and sensory uncertainty or ambiguity, the disambiguation of which requires enhanced effort.

Are there distinct patterns of co-activation with other brain regions? First, it should be noted that the interpretation of co-activation patterns is hampered by the fundamental problem that the absence of significant signal change in a particular brain region in a given study cannot be taken as evidence for the absence of a neural response in that region. This is because the fMRI signal is subject to many sources of interference, such as regional differences in vascularization, susceptibility to artifacts and spatial variability across subjects. Any comparison of activation patterns across studies should therefore be considered with caution. Yet, this does not compromise the interpretation of positive evidence of co-activations. It is striking that AIC activations in many studies reviewed here are reported as part of a large-scale network of brain regions including the dorsal ACC and/or lateral prefrontal and parietal cortices. As discussed above, the embedding into a distributed network even holds for recordings during which subjects are not engaged in any explicit functional paradigm. Fairly replicable regions in the lateral prefrontal and parietal cortex as well as along the frontal medial wall are frequently coactivated with the AIC in a wide range of cognitive tasks involving attention, working memory and response selection (Curtis and D'Esposito 2003; Ridderinkhof et al. 2004). Co-activation of AIC and dorsal ACC in particular has been attributed to emotional and autonomic processes (Critchley 2005; Craig 2009). Task-free analysis of functional connectivity analysis has provided evidence for two separate networks: an 'executive control' network including lateral prefrontal and parietal cortices and a 'salience network' comprising AIC and dorsal ACC (Seeley et al. 2007). During performance of cognitive tasks, these two networks are often co-activated, as processing of salience and executive control often coincide in such tasks. However, AIC and ACC activation often occurs in the absence of lateral prefrontal and parietal activation in tasks that do not require executive control and have been suggested to respond to a degree of personal salience that cuts across a variety of tasks independently of whether they involve a component of executive control or not (Seeley et al. 2007). Importantly, this proposal operationally defined the parameter of salience by pre-scan anxiety of subjects, which in turn opens the door for other accounts than those related to our 'perceptual' use of the salience term. Current evidence does not permit to clearly dissociate functions of AIC and ACC. Despite similarities between the two structures, however, a teleological perspective would imply that this parallel routing through both structures may serve similar, but non-identical, functional purposes that future studies should attempt to characterize. One candidate hypothesis is that these two structures play different roles in the mapping between perceptions and actions, as previously suggested (Craig 2002; Heimer and Van Hoesen 2006). The AIC may be more involved in attention and awareness, especially mediated by the representation of bodily reactions, while the ACC could serve functions more closely related to intentions and actions.

This brings us directly to the question regarding the possible connection with the AIC's role in other domains of cognitive, emotional or autonomic processing. As has been pointed out at the beginning of this study, the AIC has traditionally been thought of as a visceral sensory region. Accordingly, functional neuroimaging has provided compelling support for the eminent role of the AIC in the mapping of visceral responses and in interoceptive awareness (Craig 2002; Critchley 2005). There is now also substantial evidence for the involvement of the AIC in the subjective experience of emotional states. These include positive feelings such as those related to maternal affiliation or listening to happy voices (Bartels and Zeki 2004; Jabbi et al. 2007), negative emotional states such as pain (Peyron et al. 2000) or social exclusion (Eisenberger et al. 2003) and social emotions such as empathy (de Vignemont and Singer 2006; Sterzer et al. 2007). It has been proposed that the AIC mediates the subjective experience of feelings through the representation of physiological states, consistent with the essence of the James–Lange theory of emotions and Damasio's somatic marker hypothesis (Craig 2002; Damasio 2003; Critchley 2005). But what then is the role of AIC in perceptual tasks of minimal emotional connotation? We propose that the AIC does not play a specific role in perception. Rather, the evidence from brain imaging studies on perception suggests that the AIC is activated whenever an exogenous sensory stimulus is salient or an endogenous perceptual task is challenging. Salience, novelty or unexpectedness of the stimulus just as well as task difficulty or uncertainty in perceptual decisions can be interpreted as a challenge to homeostasis and may require the individual to change his behavior in an adaptive way.

Possibly, different parts of the AIC may be involved in different aspects of dealing with perceptual challenges and complying with action requirements. While the comparison of activation foci across the studies reviewed here does not provide a clear enough picture to make any strong conclusions about differential roles of putative AIC subregions, this is an interesting question that should be addressed in future dedicated experiments that attempt to map a functional fine-grained functional segregation within AIC. Similarly, we did not in our review observe any systematic differences between left and right AIC involvement in the perceptual paradigms reviewed here. It could be speculated that perceptual tasks that rely strongly on interoceptive feedback signals may recruit primarily the right AIC, as such laterality has repeatedly been observed in studies using interoceptive tasks (Critchley 2005). Again, this is an intriguing issue that should be explicitly addressed in future studies.

The question remains which function the AIC, a region that is primarily a sensory cortical region for interoception, might serve in perceptual processes, even if they are potentially challenging to the individuals' homeostasis. Unfortunately, any theory regarding the exact role of the AIC in perception must currently remain speculative, as direct experimental evidence is lacking. A recent model proposes a general role for the AIC in awareness (Craig 2009). According to this model, the involvement of the AIC in perceptual processes implies that the AIC supports awareness of the immediate moment with a representation of the individual's feelings about the sensory stimulus that is being processed. This is an intriguing attempt to accommodate the great number of AIC findings from neuroimaging studies on a wide variety of topics within one theory. Importantly, this model provides a conceptual framework for future research that addresses the role of AIC in perceptual processes in a hypothesis-driven fashion. However, it should not go unmentioned that current evidence permits an alternate view where virtually all AIC findings from neuroimaging research on perception to date are compatible with a purely epiphenomenal role. Thus, AIC activation could in itself be irrelevant for sensory perception, but merely reflect the central representation of increases in autonomic arousal (acceleration of heart rate, etc.) that are automatically triggered, possibly by involvement of the dorsal ACC (Critchley 2005). We cannot rule out this possibility with certainty on the basis of the current neuroimaging literature. However, neuroanatomical evidence suggests that the AIC is in an ideal situation to play an active role in modulating the processing of sensory stimuli through its direct efferent connections with all sensory cortices (Mufson and Mesulam 1982). In line with recent evidence suggesting the AIC as a central node of information convergence across different sensorimotor tasks (Ivanoff et al. 2009), we therefore favor the view that AIC plays an integrative role in perception–action coupling in that it mediates states of heightened sensory alertness and readiness for action (Fig. 3). Such heightened alertness can be driven by the salience of a sensory event, by task demands or even by spontaneous activity fluctuations. This mechanism would serve the purpose of rendering the individual more sensitive and more reactive to any kind of sensory information in situations that pose potential or actual challenges to homeostasis.

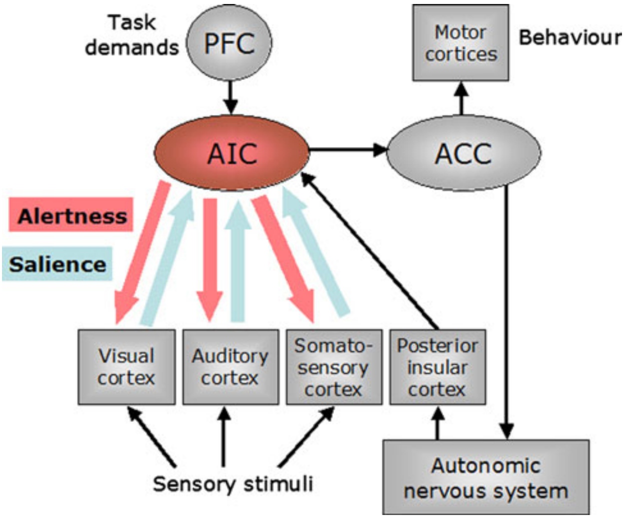

Fig. 3 A tentative model of the anterior insula's role in perception. Anterior insular cortex is activated whenever an exogenous sensory stimulus is salient or an endogenous task is challenging, and mediates states of heightened sensory alertness via feedback connections to sensory cortices. This mechanism renders the individual more sensitive to any kind of sensory information in situations that pose potential or actual challenges to homeostasis. The interoceptive representation of autonomic bodily reactions in anterior insular cortex is crucially involved in generating a state of heightened sensory alertness. The functional role of the anterior insula is intricately linked to that of the anterior cingulate cortex, which plays a central role in initiating and regulating adaptive changes in autonomic nervous system activity and motor behavior. *AIC* anterior insular cortex, *ACC* anterior cingulate cortex, *PFC* prefrontal cortex

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