Functional Neuroimaging Studies of Human Emotions

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FOCUS POINTS

- While the preponderance of evidence supports the role of the amygdala in fear processing, some data suggests that it also responds to general negative/aversive and positive/appetitive stimuli.
- The medial prefrontal cortex is commonly activated in studies of emotion, and may be involved in general processes, including emotion evaluation, experience, and regulation.
- Activity in the subcallosal/subgenual cingulate cortex is associated with both the perception of sad facial emotions and the experience of sadness.
- Functional neuroimaging techniques provide useful tools to test hypotheses derived from animal and human lesion studies.

ABSTRACT

Neuroimaging studies with positron emission tomography and functional magnetic resonance imaging have begun to describe the functional neuroanatomy of human emotion. Taken separately, specific studies vary in task dimensions and in type(s) of emotion studied, and are limited by statistical power and sensitivity. By examining findings across studies in a meta-analysis, we sought to determine if common or segregated patterns of activations exist in different emotions and across various emotional tasks. We surveyed over 55 positron emission tomography and functional magnetic resonance imaging activation studies, which investigated emotion in healthy subjects. This paper will review observations in several regions of interest in limbic (eg, amygdala, anterior cingulate cortex) and paralimbic (eg, medial prefrontal cortex, insula) brain regions in emotional responding.

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INTRODUCTION

The investigation of the neural basis of emotion has gained considerable interest recently. Traditionally, the neural substrates of emotion and emotional processing have been defined by models based on animal and brain lesion studies,[1-3] which largely implicate the limbic system. Recently, the investigation has been aided by the emergence of functional neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), which can test hypotheses about the neural substrates of emotion in healthy individuals. Imaging studies examine emotion-related activity in the brain by increases in regional cerebral blood flow or blood-oxygen level-dependent (BOLD) signal as markers of neuronal activity. Specific brain regions have been hypothesized to have specialized functions for emotional operations. For example, the amygdala is postulated to be critical to fear-related processing,[4] that its activity reflects dispositional affective style.[5] The medial prefrontal cortex has been hypothesized to have specific roles for emotion-related decision making[6] and emotional self-regulation.[7] The insula is thought of as the brain's "alarm center," integrating internal somatic cues with emotional experience,[8] and has been linked specifically to disgust.[9] In spite of general agreement about some of these specialized "emotional" regions, conflicting findings are

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often produced by studies using different induction methods and imaging techniques.

This article presents an overview of recent findings on the functional neuroanatomy of emotion referring, where relevant, to animal and lesion studies that provide support for imaging findings. We summarize here relevant findings of two comprehensive meta-analyses[10,11] of PET and fMRI studies of emotion in which we examined findings of over 55 functional imaging studies spanning a decade of in vivo brain imaging of emotion. The analyses included studies of healthy adults across a wide variety of specific emotions (fear, sadness, disgust, anger, happiness) and emotional dimensions (negative/aversive or positive/appetitive) across all modalities of emotion induction/evocation (visual, auditory, or emotional recall/imagery). In this article, we highlight potential functional roles for several limbic (eg, amygdala, anterior cingulate cortex) and paralimbic (eg, medial prefrontal cortex, insula) brain regions. While other brain regions were observed to be activated in several neuroimaging studies (eg, occipital cortex, basal ganglia, etc.), we focused these regions because they reflect the primary findings from our two meta-analyses[10,11] and traditionally have been implicated in prior reviews of the functional brain anatomy of emotion based on both human and animal studies.[4,5,12-17]

SUMMARY OF FINDINGS

Amygdala

The foremost brain region implicated in emotion is the amygdala, positioned within the medial portion of the temporal lobe. Based on animal studies, the amygdala is posited to be involved in fear-related responding.[3,4] We found support of this hypothesis from human imaging studies such that stimuli that signal threat (eg, fearful faces) had a strong association with the amygdala. Over 60% of studies that examined fear activated the amygdala (Figure 1). Several lines of evidence support the notion that the amygdala is responsible for detecting, generating, and maintaining fear-related emotions. Based on both animal work, human lesion, and imaging studies, the amygdala has been consistently implicated in fear conditioning,[4,18] the recognition of fearful facial expressions,[19,20] feelings of fear after procaine induction,[21] and the evocation of fearful emotional responses from direct stimulation.[22] The amygdala also appears important in the detection of environment threat,[23-25] as well as in the coordination of appropriate responses to threat and danger.[26-28] Of the eight studies[9,25,29-34] that examined cerebral responses to fearful faces, six pointed to the critical involvement of the amygdala. Fear-associated amygdalar activations also extended into other modalities such as words[24] and vocalizations.[25] Morris and colleagues[29] found that the amygdalar response to fearful faces showed a significant interaction with the intensity of emotion (increasing with increasing fearfulness).

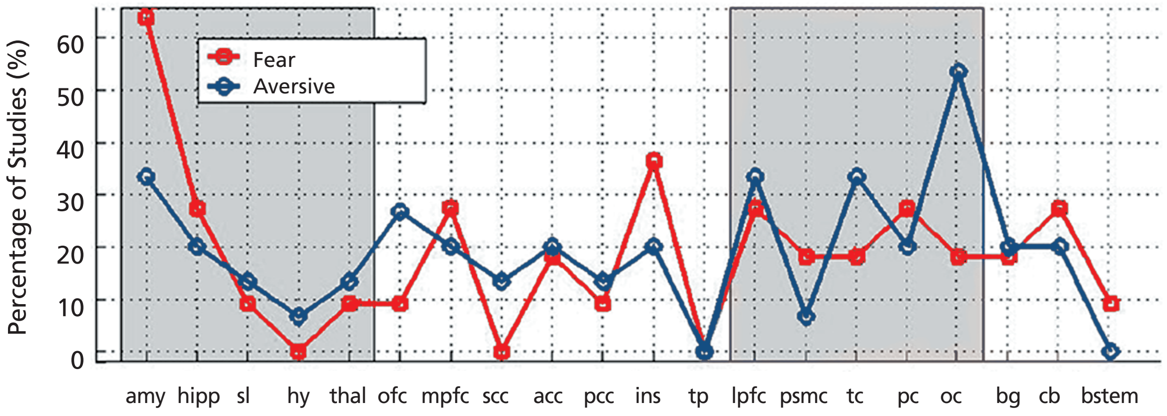

FIGURE 1. Frequency of reported activations (expressed as percentage of studies) in response to stimuli with fear-related (11 studies) and aversive (15 studies) content in 20 regions of interest.

amy=amygdala; hipp=hippocampus; sl=sublenticulum; hy=hypothalamus; thal=thalamus; ofc=orbitofrontal cortex; mpfc=medial prefrontal cortex; scc=subcallosal cingulate cortex; pcc=posterior cingulate cortex; ins=insula; tp=temporal pole; lpfc=lateral prefrontal cortex; psmc=primary sensory-motor cortex; tc=temporal cortex; pc=parietal cortex; oc=occipital cortex; bg=basal ganglia; cb=cerebellum; bstem=brain stem.

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The activation was not contingent upon the explicit processing of facial expression, as subjects were instructed to classify emotional faces by gender not by emotion. Such an interpretation is further strengthened by findings from studies using masked fearful faces which found that the amygdalar response occurred even when the fearful expression was not consciously perceived or even when subjects did not experience fear subjectively.[31,32]

Because fear may be the most salient of the individual emotions, an alternative interpretation for the amygdala's involvement is that it has a more general role for vigilance or for processing salience, or attributes that make stimuli meaningful,[13] Whalen and colleagues[32] observed that the amygdala responds to fearful faces despite the lack of explicit recognition of the expression, and that fearful faces are more likely to signify a signal for threat than to induce actual fear. In the controlled laboratory environment, most subjects do not report being afraid of fearful face stimuli. Hence, the amygdalar activations may serve to signal threat, rather than evoke emotions of fear, and may serve a more general function to alert the organism towards salient cues. For example, the amygdala has been shown to govern judgments about the extent of trustworthiness as judged from facial expressions.[35,36] Moreover, the amygdala activation has been observed during the processing of racial outgroup versus ingroup face stimuli,[37] and has been correlated with performance on indirect measures (eg, implicit association test and potentiated startle) of race evaluation (black versus white faces).[38] Since evoked fear is concurrent with increased arousal, activation of the amygdala may also be related to a general response to the emotional intensity of stimuli. Recent observations have noted that activity in the amygdala to emotional events correlates with perceived subjective emotional arousal/intensity[39,40] or physiologic arousal.[41] In support, studies that use stimuli which evoke more general aversive/negative emotional experience (eg, not necessarily fear), have also observed amygdala activation,[42, 43] though that activation may be less pronounced than to faces expressing fear (Figure 1).[10,43] However, activation of the amygdala may also not be specific to fear-related or negative or withdrawal-related emotions. For example, amygdala activations occur to various to positive or pleasant stimuli, such as happy faces.[30] Several studies[44-48] that have reported amygdalar responses to both positive/appetitive and negative/aversive stimuli. Thus, the amygdala may not exclusively respond to a particular valence, but may respond more generally to salient characteristics of emotional stimuli.

Left-lateralization of amygdala function in emotion studies has been proposed by several groups, based on findings from both lesion patients and imaging studies.[49-54] Morris and colleagues[52] have proposed that stimuli processed below the level of awareness activate the right amygdala, whereas consciously processed emotional stimuli preferentially activates the left amygdala. The lateralization of amygdala response has been hypothesized to reflect differential phasic and tonic (eg, sustained) activity over time.[51,54] The majority of studies covered in our two published meta-analyses have used explicit, conscious presentation of stimuli, which might account for the left-sided predominance of activation. In contrast, Whalen and colleagues[55] have found bilateral amygdala activation using masked presentations of fearful faces, presumably below the level of subjective awareness. Recently, several groups have reported that lateralization of amygdala activations may be related to sex/gender differences. Cahill and colleagues[56] found that right amygdala activity evoked by emotionally negative films correlated with memory for the films in men and left amygdala activity correlated with memory performance in women. Killgore and Yurgelun-Todd[51] found left lateralization of amygdala activity induced by happy faces for men only, and left lateralization for fearful faces in both sexes. While our meta-analysis did not find evidence for these effects in the amygdala proper,[11] we found left-lateralized activations in the extended amygdala in females and right-sided lateralization in the hippocampus in men, indicating that emotion-memory circuits in the limbic system may be activated differently for men and women. Interestingly, the temporal cortex exhibits some of the more robust differences in resting metabolism between men and women, with men showing greater relative resting metabolism in lateral and ventromedial temporal lobe and greater raw absolute metabolic rates in the temporal pole, hippocampus, and amygdala.[57] Additional evidence will be necessary to clarify the effect of time-course, level of conscious awareness, and gender on lateralization of amygdala activity.

Another current topic of investigation involves the extent to which amygdalar activity can be influenced by cognitive activity as reflected in specific task requirements, available attentional resources, or cognitive modulation. The amygdala has been hypothesized to be involved in automatic or involuntary responses to emotionally salient stimuli.[3] Conscious and unconscious perception of faces with fearful expressions elicit significant amygdala responses, supporting an automated engagement to meaningful environmental cues.[31,32] Such an involuntary reaction conveys adaptive advantage for successful coordination of appropriate responses, including avoidance behaviors, enhancement of emotional perception[49] and memory.[39,44,58] for emotionally salient material.

Recent observations suggest that "top-down" cognitive processes, such as attention or emotional regulation, can mediate the amygdala response. A different but complementary model proposes that activity in the amygdala (and other limbic regions) can be modulated based on task demands or cognitive influences. Prior findings[59] in our laboratory are also consistent with the notion that task demands can attenuate the amygdala response. Our laboratory observed an increase in activity in the extended amygdala (a structure anatomically continuous with amygdala proper within the basal forebrain that links the centromedial amygdala to the bed nucleus of stria terminalis), when subjects shifted from performing a recognition and emotional recall task to an emotional rating task while viewing pictures.[60] Tasks requiring increased cognitive effort (eg, appraising stimulus content for personal relatedness) that does not necessarily redirect attention away from the emotional content can also reduce limbic responses.[59] Ochsner and colleagues[61] had subjects reappraise negative pictures with various cognitive strategies and found that this process (relative to simply attending to the stimulus) reduced activity in the amygdala. In our meta-analysis,[10] we noted that studies which employed a cognitive task during affective processing were ~15% less numerous in demonstrating activity in subcortical limbic regions, including the amygdala. In two separate studies, Hariri and colleagues[62,63] found that when processing emotional faces and pictures the more cognitively demanding task of labeling the emotional content reduced activation in the amygdala, relative to a simple stimulus matching or emotion perception task. Lange and colleagues[63] found that passive viewing of fearful faces activated the amygdala in contrast to gender or affect identification.

It is important to note that prior imaging studies that had implicated implicit, task-independent processing in the amygdala involved perception of emotional faces, not pictures.[32,36,64] Emotional faces and pictures may have divergent routes or evoke different intensity of response from the amygdala,[10,43] which may explain these prior observations that the amygdala may have more "automatic" responses to certain salient stimuli. In support of this hypothesis, a recent report demonstrated that the amygdala is best activated by faces when the emotional content is not the focus of attention, whereas it is more responsive to salient pictures when the emotional content is the focus of attention.[65] Pessoa and colleagues[66] examined brain regions that respond automatically (eg, without explicit, volitional control) to emotional stimuli and found that the amygdala was only activated when sufficient attentional resources were available to process the stimuli, suggesting that activity in this region is modulated by attentional demand and is under top-down control. In their examination of the automaticity of amygdala response to signals of threat, Anderson and colleagues[67] reported that while amygdala activation to faces of fear was not affected by reduced attention, it was not entirely automatic. Moreover, amygdala activation was enhanced with reduced attention to faces of disgust, suggesting differential responses based on the type of salient information.[67] These findings suggest that attentional resources and cognitive activity may have some influence on amygdala activity, and that further study is needed to clarify the automaticity of the amygdala response to salient information.

Medial Prefrontal Cortex

No specific brain region was consistently activated in the majority of imaging studies of emotion, across individual emotions and induction methods, suggesting that no single brain region is commonly activated by all emotional tasks. However, we did find that the paralimbic medial prefrontal cortex (MPFC; Brodmann Areas [BAs][8-10] otherwise known as the frontomedian cortex) was activated in nearly 50% of all studies, and that its activation was not specific to a specific emotion (Figure 2). While there may not be a particular brain region that is absolutely necessary for all emotional functions, the common activation of the MPFC may reflect aspects shared across different emotional tasks. These findings suggest that the MPFC may have a "general" role in emotional processing (eg, appraisal/evaluation, experience, response), as suggested by Lane and colleagues[68,69] and Reiman and colleagues,[70] who reported that emotional films, pictures, and recall as wells as positive and negative emotion, happiness, sadness, disgust, and the mixture of these emotions all separately engaged the MPFC. One possibility, therefore, is that the MPFC may be involved in the cognitive aspects (eg, attention to emotion, appraisal/identification of emotion, awareness of emotion) that is closely intertwined with emotional processing.[71] Such a general function in emotion can be related to self-referential processing about one's own emotional experience. Several studies[71-75] have been recently published demonstrating that when subjects turn their attention inward toward themselves, as often required during general emotional processing, activity within MPFC is increased. Studies[73,74] requiring subjects to determine if personality trait adjectives are descriptive of themselves (versus someone else) or to reflect on their own abilities/traits/attitudes have observed engagement of the MPFC. Other related paradigms involve subjects making introspective judgments about their emotional experience (evoked feelings of unpleasantness) while viewing salient pictures have also demonstrated MPFC activity.[72,76] The view that the MPFC plays a prominent role in self-referential activity is also supported by neuropsychological evidence. A lack of self-reflection, introspection, and self-awareness have been long associated with persons with damage to the MPFC. This damage appears to impair their ability to reflect on personal knowledge or to make personally advantageous decisions based on emotional cues.[6,8]

Activation of the MPFC could also involve the regulation of emotional states, as often required to generate responses that are contextually appropriate. If responses in the amygdala to emotional evocation can be modulated by cognitive tasks, prefrontal regions may be well positioned to serve as modulators of limbic activity. The MPFC, with extensive connections to subcortical limbic structures including the amygdala, constituting a "paralimbic" cortex, comprise a plausible interaction zone between affective and cognitive processing.[71,77] Given its connections to subcortical limbic structures, the MPFC could serve as a "top-down" modulator of intense emotional responses, especially those generated by the amygdala. Several lines of evidence support such an interpretation. From animal studies,[3] the amygdala has been shown

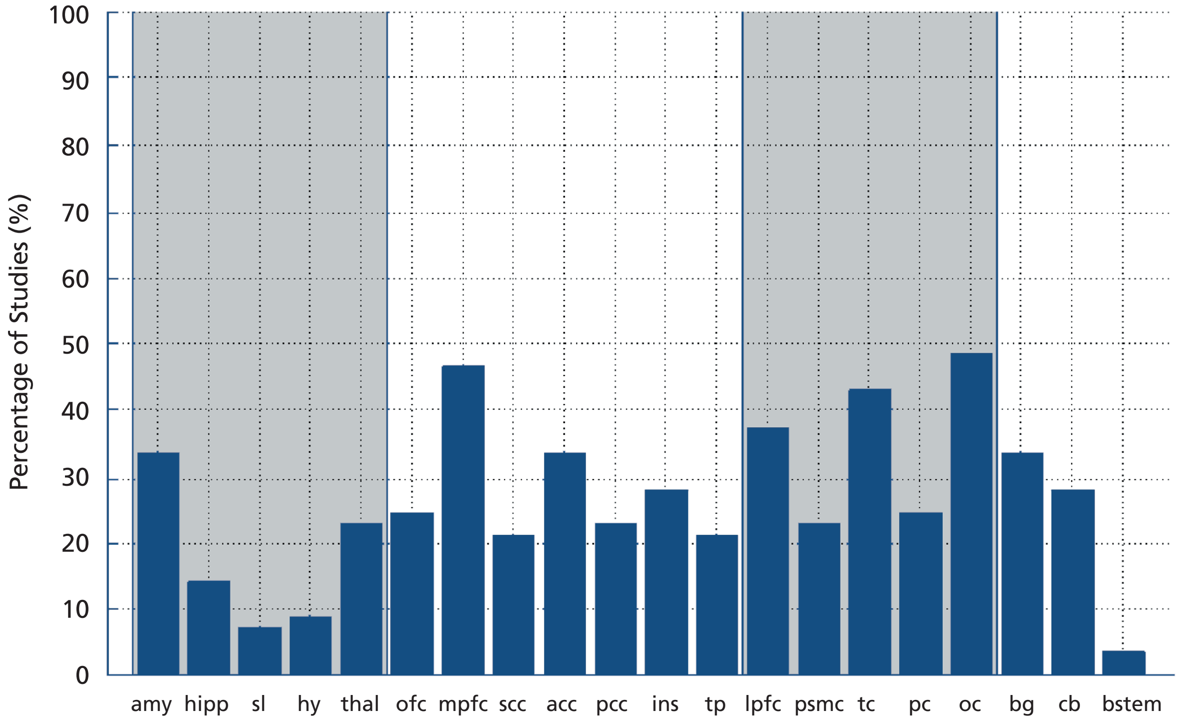

FIGURE 2. Frequency of reported activations (expressed as percentage of studies) in response to all types of emotion(s) and emotional stimuli/induction method across 20 regions of interest.

amy=amygdala; hipp=hippocampus; sl=sublenticulum; hy=hypothalamus; thal=thalamus; ofc=orbitofrontal cortex; mpfc=medial prefrontal cortex; scc=subcallosal cingulate cortex; pcc=posterior cingulate cortex; ins=insula; tp=temporal pole; lpfc=lateral prefrontal cortex; psmc=primary sensory-motor cortex; tc=temporal cortex; pc=parietal cortex; oc=occipital cortex; bg=basal ganglia; cb=cerebellum; bstem=brain stem.

Phan KL, Wager TD, Taylor SF, Liberzon I. *CNS Spectr*. Vol 9, No 4. 2004 to be critical in fear conditioning. Conditioned fear can be interfered with by ablation of the MPFC.[78] Lesions in the human rostral MPFC also lead to socially inappropriate expressions of emotions and impairments in interpreting personally-advantageous cues,[6] suggesting a lack of cognitive processing of emotionally "loaded" situations. Furthermore, glucose metabolism in the MPFC is inversely associated with the glucose metabolic rate of the amygdala.[79] Our group[58] has found that activity is the amygdaloid region is attenuated while the MPFC and cingulate sulcus are activated during a cognitive appraisal condition of aversive visual stimuli (versus passive viewing) and that activity in MPFC is inversely related to that within the amygdala during emotional experience.[80] Recent studies[61,81] that examine brain activation from cognitive reappraisal (an emotion regulation strategy) and or cognitive volitional inhibition of emotionally evocative stimuli have observed engagement of the medial prefrontal cortex. Deactivation of the amygdala has been observed in several tasks that involve higher cognitive processing and MPFC activity.[71] On the other hand, an alternative hypothesis to prefrontal modulation of amygdala activity is that the amygdala may respond more to stimuli that are more "emotive" at a sensory/perceptual level, and are less likely to be engaged by cognitively demanding emotional tasks, or to cognitively elicited emotions.[70,82]

Anterior Cingulate Cortex

The anterior cingulate cortex (BAs 24–25, 32–33) is broadly described as belonging to the limbic lobe, given its expensive connections to subcortical structures such as the amygdala.[83] Several investigators have suggested a functional segregation, whereby the more dorsal division is involved in cognitive tasks while the more rostral-ventral affective division (ACad) serves emotional functions.[12] Lesion to the anterior cingulate cortex (ACC) result in a variety of emotional disturbances including apathy, and emotional instability.[83] Together, the ACC is known to be involved in a form of attention that serves to regulate both cognitive and emotional processing,[12,84] and is closely interconnected to frontal regions including ventral-rostral BAs 9 and 10 of the MPFC. Therefore, the ACad may interact with the MPFC to regulate tasks with cognitive and affective components during an emotional response. More generally, the ACad is posited to be involved in the assessment of salience in motivational and emotional information and the regulation of emotional responses.[12] The rostral ACC has also been linked to the mediation of emotional arousal,[85,86] and its activity appears to be more pronounced when external information requires additional processing with conflicting internal states.[85] Furthermore, activity in the ACC (BA 24) has been shown to correlate with emotional awareness to both film and recall-generated emotion, suggesting its role in detecting emotional signals from both exteroceptive and interoceptive cues.[87] Lane and colleagues[77] also reported that the rostral ACC (BA 32) activated when subjects attended to their internal, emotional state, but not when they attended to external, non-affective characteristics of a picture stimulus, such as deciding whether a scene was indoors or outdoors. As a detector of salient information in general, the ACC could serve to allocate brain resources, heighten sensitivity and direct attention to environmental cues produced by the evocative stimulus.[87,88]

One specific emotion, sadness, was particularly associated with a region within the ACC, namely the subcallosal cingulate cortex (SCC). Approximately 46% of sadness induction studies reported activation of the ventral/subgenual anterior cingulate (BA 25) in the SCC, over twice as frequently as any other specific emotion. Interestingly, alterations in SCC activity has been found in resting state studies of patients with clinical depression, a mood disorder characterized by sustained sadness.[89-91] Specifically within the pregenual ACC, physiological activity appears to be elevated during the depressed phase of some major depressive disorder subtypes.[92,93] Activity in the subgenual cingulate (BA 25) appears to normalized when depressed subjects respond to pharmacologic treatment.[93]

Tasks inducing emotions in subjects often do so by having them evoke memories or imagery of personally relevant affectively laden autobiographical life vents that do require explicit intensive cognitive effort. Accordingly, the recollection/recall induction of emotion specifically activated the anterior cingulate; 50% of recall induction studies reported ACC activations, versus 31% and 0% of visual and auditory-based emotion studies, respectively. Cognitive tasks often engage the ACC[94] and, therefore, this association suggests that recalled emotions involve cognitive activity, as noted by Reiman and colleagues[70] and Teasdale and colleagues.[82] Given its known cognitive functions including modulation of attention and executive functions, and interconnections with subcortical limbic structures, the ACC's involvement in cognitive induction of emotional response is not surprising. Such a process demands cognitive effort, as subjects are instructed to recall or imagine an emotionally laden personal event then self-induce or internally generate intense target emotions.[82]

Insula

Besides the ACC, we also found that 60% of studies on emotional recall reported activation of the insula compared with other emotion induction paradigms. Lane and colleagues[69] and Reiman and colleagues[70] specifically found that emotional recall, but not emotional film viewing, engaged the insula. Our findings as well as earlier studies on non-human primates[95] support the notion that the insula is preferentially involved in the evaluative, experiential, or expressive aspects of "internally generated" emotions.[70] Anatomically, the insula shares connections with the amygdala. Through these pathways, the insula relays interoceptive information to the amygdala and can communicate information based on internal somatic sensations evoked by emotional stimuli.[95,96]

Although earlier imaging evidence had implicated the insula as a specific neural substrate for disgust,[9] meta-analysis did not show that disgust was significantly associated with insular activation. In other words, the insula was activated in other types of emotions besides disgust. In support, recent studies have observed that the insula responds more generally to aversive or threat-related processing, including not only disgust but also fear.[97] Animal studies have demonstrated that the insula is important for conditioned aversive responses, and recent human imaging studies[96] link it the perception and experience of pain and anticipatory anxiety and other general negative emotional states, such as guilt.[98] These findings point to the role of the insula as mediating responses to aversive or withdrawal-inducing stimuli. The essence of the "somatic-marker" hypothesis, as proposed by Damasio,[6,8] suggests that the insula might integrate emotionally relevant information between somatic internal feelings with external cues. Such a process is evolutionarily adaptive in the service of providing a basis for implicit awareness of the physical self across time. These involuntary "gut feelings" help to guide behavioral decisions via a "perceptual landscape" that represents the emotional significance of a particular stimulus that is being experienced. Accordingly, Reiman and colleagues[70] has posited that the insula may participate in the evaluation of "interoceptive emotional significance" as an alarm center for internally sensed dangers or homeostatic changes. Such an "internal alarm" hypothesis is consistent with our finding that insular activity is increased in response to all aversive stimuli that evoke visceral/somatic sensations.

CONCLUSION

Using data obtained from our two recent meta-analyses of the functional neuroanatomy of emotion based on in vivo brain imaging studies. The emerging findings suggest that several discrete brain regions are involved in specific emotions or emotional tasks, while others were more involved in general emotion perception/evaluation or regulation without regard to a specific emotional state. Many of these implicated areas and their putative functional roles are consistent with data previously provided from anatomic descriptions, animal experiments, and human lesion studies. Though future neuroimaging studies will no doubt add to our current understanding functional brain segregation and connectivity for emotional operations, the patterns and regions identified in this overview and our meta-analyses[10,11] appear to be important constituents of the functional neuroanatomy of emotion. Future studies with more advanced imaging techniques and novel analytic methods that build on these emerging findings will be instrumental in exploring how these, and other, brain regions may be functionally connected in an "emotion network" in the human brain. CNS

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