

# Functional Neuroimaging Studies of Human Emotions

By K. Luan Phan, MD, Tor D. Wager, PhD,  
Stephan F. Taylor, MD, and Israel Liberzon, MD

## 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.*

*CNS Spectr. 2004;9(4):258-266*

## 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,<sup>1-3</sup> 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,<sup>4</sup> that its activity reflects dispositional affective style.<sup>5</sup> The medial prefrontal cortex has been hypothesized to have specific roles for emotion-related decision making<sup>6</sup> and emotional self-regulation.<sup>7</sup> The insula is thought of as the brain's "alarm center," integrating internal somatic cues with emotional experience,<sup>8</sup> and has been linked specifically to disgust.<sup>9</sup> In spite of general agreement about some of these specialized "emotional" regions, conflicting findings are

*Dr. Phan is assistant professor of psychiatry and behavioral neurosciences and director of the Anxiety Disorders Imaging Laboratory in the Brain Imaging Research Division of the Department of Psychiatry and Behavioral Neurosciences at the School of Medicine, Wayne State University in Detroit, Michigan. Dr. Wager is assistant professor of psychology in the Department of Psychology at Columbia University in New York City. Dr. Taylor is assistant professor of psychiatry in the Department of Psychiatry at the University of Michigan Medical School in Ann Arbor. Dr. Liberzon is associate professor of psychiatry and co-director of the Trauma, Stress, and Anxiety Research Center in the Department of Psychiatry at the University of Michigan Medical School.*

*Disclosure: The authors do not have an affiliation with or financial interest in a commercial organization that might pose a conflict of interest.*

*Please direct all correspondence to: K. Luan Phan, MD, Wayne State University, School of Medicine, Department of Psychiatry & Behavioral Neurosciences, 4201 St. Antoine, UHC-9B-18, Detroit, MI 48201.*

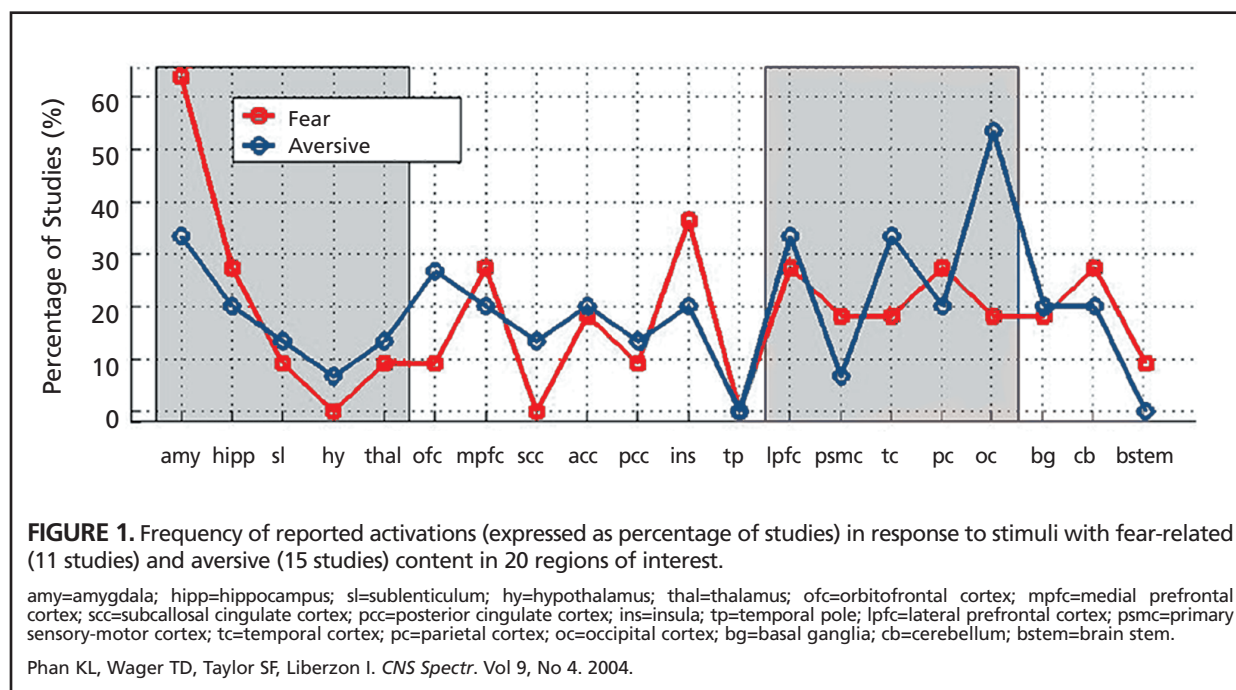
often produced by studies using different induction methods and imaging techniques.

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<sup>10,11</sup> 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<sup>10,11</sup> and traditionally have been implicated in prior reviews of the functional brain anatomy of emotion based on both human and animal studies.<sup>4,5,12-17</sup>

## 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.<sup>3,4</sup> 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,<sup>4,18</sup> the recognition of fearful facial expressions,<sup>19,20</sup> feelings of fear after procaine induction,<sup>21</sup> and the evocation of fearful emotional responses from direct stimulation.<sup>22</sup> The amygdala also appears important in the detection of environment threat,<sup>23-25</sup> as well as in the coordination of appropriate responses to threat and danger.<sup>26-28</sup> Of the eight studies<sup>9,25,29-34</sup> 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<sup>24</sup> and vocalizations.<sup>25</sup> Morris and colleagues<sup>29</sup> found that the amygdalar response to fearful faces showed a significant interaction with the intensity of emotion (increasing with increasing fearfulness).



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.<sup>31,32</sup>

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.<sup>13</sup> Whalen and colleagues<sup>32</sup> 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.<sup>35,36</sup> Moreover, the amygdala activation has been observed during the processing of racial outgroup versus ingroup face stimuli,<sup>37</sup> and has been correlated with performance on indirect measures (eg, implicit association test and potentiated startle) of race evaluation (black versus white faces).<sup>38</sup> 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<sup>39,40</sup> or physiologic arousal.<sup>41</sup> In support, studies that use stimuli which evoke more general aversive/negative emotional experience (eg, not necessarily fear), have also observed amygdala activation,<sup>42, 43</sup> though that activation may be less pronounced than to faces expressing fear (Figure 1).<sup>10,43</sup> 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.<sup>30</sup> Several studies<sup>44-48</sup> 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.<sup>49-54</sup> Morris and colleagues<sup>52</sup> 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.<sup>51,54</sup> 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<sup>55</sup> 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<sup>56</sup> 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<sup>51</sup> 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,<sup>11</sup> 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.<sup>57</sup> 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.<sup>3</sup> Conscious and unconscious perception of faces with fearful expressions elicit significant amygdala responses, supporting an automated engagement to meaningful environmental cues.<sup>31,32</sup> Such an involuntary reaction conveys adaptive advantage for successful coordination of appropriate responses, including avoidance behaviors, enhancement of emotional perception<sup>49</sup> and memory.<sup>39,44,58</sup> 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<sup>59</sup> 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.<sup>60</sup> 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.<sup>59</sup> Ochsner and colleagues<sup>61</sup> 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,<sup>10</sup> 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<sup>62,63</sup> 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<sup>63</sup> 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.<sup>32,36,64</sup> Emotional faces and pictures may have divergent routes or evoke different intensity of response from the amygdala,<sup>10,43</sup> 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.<sup>65</sup> Pessoa and colleagues<sup>66</sup> 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<sup>67</sup> 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.<sup>67</sup> 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.

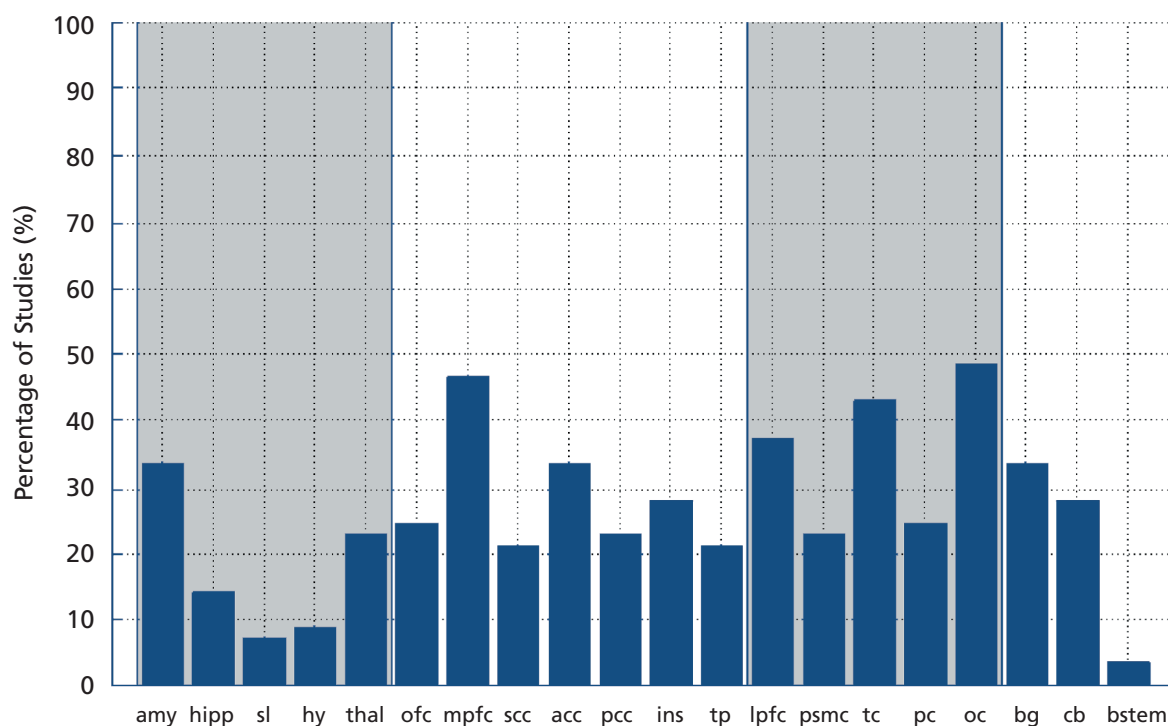
### **Medial Prefrontal Cortex**

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]<sup>8-10</sup> 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<sup>68,69</sup> and Reiman and colleagues,<sup>70</sup> who reported that emotional films, pictures, and recall as well 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.<sup>71</sup> Such a general function in emotion can be related to self-referential processing about one's own emotional experience. Several studies<sup>71-75</sup> 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<sup>73,74</sup> 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.<sup>72,76</sup> 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.<sup>6,8</sup>

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.<sup>71,77</sup> 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,<sup>3</sup> 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=sublenticle; 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.<sup>78</sup> Lesions in the human rostral MPFC also lead to socially inappropriate expressions of emotions and impairments in interpreting personally-advantageous cues,<sup>6</sup> 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.<sup>79</sup> Our group<sup>58</sup> has found that activity in 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.<sup>80</sup> Recent studies<sup>61,81</sup> 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.<sup>71</sup> 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.<sup>70,82</sup>

### **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.<sup>83</sup> 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.<sup>12</sup> Lesion to the anterior cingulate cortex (ACC) result in a variety of emotional disturbances including apathy, and emotional instability.<sup>83</sup> Together, the ACC is known to be involved in a form of attention that serves to regulate both cognitive and emotional processing,<sup>12,84</sup> 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.<sup>12</sup>

The rostral ACC has also been linked to the mediation of emotional arousal,<sup>85,86</sup> and its activity appears to be more pronounced when external information requires additional processing with conflicting internal states.<sup>85</sup> 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.<sup>87</sup> Lane and colleagues<sup>77</sup> 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.<sup>87,88</sup>

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.<sup>89-91</sup> Specifically within the pregenual ACC, physiological activity appears to be elevated during the depressed phase of some major depressive disorder subtypes.<sup>92,93</sup> Activity in the subgenual cingulate (BA 25) appears to normalized when depressed subjects respond to pharmacologic treatment.<sup>93</sup>

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<sup>94</sup> and, therefore, this association suggests that recalled emotions involve cognitive activity, as noted by Reiman and colleagues<sup>70</sup> and Teasdale and colleagues.<sup>82</sup> Given its known cognitive functions including modulation of attention and executive functions, and interconnections with subcortical limbic structures, the ACC’s involvement in cogni-

tive 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.<sup>82</sup>

## 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<sup>69</sup> and Reiman and colleagues<sup>70</sup> specifically found that emotional recall, but not emotional film viewing, engaged the insula. Our findings as well as earlier studies on non-human primates<sup>95</sup> support the notion that the insula is preferentially involved in the evaluative, experiential, or expressive aspects of “internally generated” emotions.<sup>70</sup> 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.<sup>95,96</sup>

Although earlier imaging evidence had implicated the insula as a specific neural substrate for disgust,<sup>9</sup> 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.<sup>97</sup> Animal studies have demonstrated that the insula is important for conditioned aversive responses, and recent human imaging studies<sup>96</sup> link it the perception and experience of pain and anticipatory anxiety and other general negative emotional states, such as guilt.<sup>98</sup> 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,<sup>6,8</sup> 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<sup>70</sup> 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<sup>10,11</sup> 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**

## REFERENCES

1. Papez JW. A proposed mechanism of emotion. *Arch Neurol Psychiatry*. 1937;38:725-743.
2. MacLean PD. Some psychiatric implications of physiological studies on the frontotemporal portion of the limbic system. *Electroencephalogr Clin Neurophysiol*. 1952;4:407-418.
3. LeDoux JE. *The Emotional Brain*. New York, NY: Touchstone; 1996.
4. LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci*. 2000;23:155-184.
5. Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci*. 1999;3:11-21.
6. Damasio AR. *Descartes' Error*. New York, NY: Avon Books, Inc.; 1994.
7. Davidson RJ, Jackson DC, Kalin NH. Emotion, plasticity, context, and regulation: perspectives from affective neuroscience. *Psychol Bull*. 2000;126(spec. issue):890-909.
8. Damasio AR. *The Feeling of What Happens: Body and Emotion in the Making of Consciousness*. New York, NY: Harcourt Brace; 1999.
9. Phillips ML, Young AW, Senior C, et al. A specific neural substrate for perceiving facial expressions of disgust. *Nature*. 1997;389:495-498.
10. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*. 2002;16:331-348.
11. Wager TD, Phan KL, Liberzon I, Taylor SF. Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. *Neuroimage*. 2003;19:513-531.
12. Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci*. 2000;4:215-222.

13. Davis M, Whalen PJ. The amygdala: vigilance and emotion. *Mol Psychiatry*. 2001;6:13-34.
14. Zald DH. The human amygdala and the emotional evaluation of sensory stimuli. *Brain Res Brain Res Rev*. 2003;41:88-123.
15. Rolls ET. Precis of The brain and emotion. *Behav Brain Sci*. 2000;23:177-191.
16. Critchley H. Emotion and its disorders. *Br Med Bull*. 2003;65:35-47.
17. Phillips ML, Drevets WC, Rauch SL, Lane R. The neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biol Psychiatry*. 2003;54:504-514.
18. Buchel C, Dolan RJ. Classical fear conditioning in functional neuroimaging. *Curr Opin Neurobiol*. 2000;10:219-223.
19. Adolphs R, Tranel D, Damasio H, Damasio AR. Fear and the human amygdala. *J Neurosci*. 1995;15:5879-5891.
20. Adolphs R, Tranel D, Hamann S, et al. Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia*. 1999;37:1111-1117.
21. Ketter TA, Andreason PJ, George MS, et al. Anterior paralimbic mediation of procaine-induced emotional and psychosensory experiences. *Arch Gen Psychiatry*. 1996;53:59-69.
22. Halgren E, Walter RD, Cherlow DG, Crandall PH. Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdala. *Brain*. 1978;101:83-117.
23. Scott SK, Young AW, Calder AJ, Hellawell DJ, Aggleton JP, Johnson M. Impaired auditory recognition of fear and anger following bilateral amygdala lesions. *Nature*. 1997;385:254-257.
24. Isenberg N, Silbersweig D, Engelen A, et al. Linguistic threat activates the human amygdala. *Proc Natl Acad Sci U S A*. 1999;96:10456-10459.
25. Phillips ML, Young AW, Scott SK et al. Neural responses to facial and vocal expressions of fear and disgust. *Proc R Soc Lond B Biol Sci*. 1998;265:1809-1817.
26. Kluver H, Bucy PC. Preliminary analysis of functions of the temporal lobes in monkeys. *Arch Neurol Psychiatry*. 1939;42:979-1000.
27. Weiskrantz L. Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *J Comp Physiol Psychol*. 1956;49:381-391.
28. King SM, Cowey A. Defensive responses to looming visual stimuli in monkeys with unilateral striate cortex ablation. *Neuropsychologia*. 1992;30:1017-1024.
29. Morris JS, Frith CD, Perrett DI, et al. A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature*. 1996;383:812-815.
30. Breiter HC, Etcoff NL, Whalen PJ, et al. Response and habituation of the human amygdala during visual processing of facial expression. *Neuron*. 1996;17:875-887.
31. Morris JS, Ohman A, Dolan RJ. Conscious and unconscious emotional learning in the human amygdala. *Nature*. 1998;393:467-470.
32. Whalen PJ, Rauch SL, Etcoff NL, McNerney SC, Lee MB, Jenike MA. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci*. 1998;18:411-418.
33. Phillips ML, Medford N, Young AW, et al. Time courses of left and right amygdalar responses to fearful facial expressions. *Hum Brain Mapp*. 2001;12:193-202.
34. Whalen PJ, Rauch SL, Etcoff NL, McNerney SC, Lee MB, Jenike MA. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci*. 1998;18:411-418.
35. Adolphs R, Tranel D, Damasio AR. The human amygdala in social judgment. *Nature*. 1998;393:470-474.
36. Winston JS, Strange BA, O'Doherty J, Dolan RJ. Automatic and intentional brain responses during evaluation of trustworthiness of faces. *Nat Neurosci*. 2002;5:277-283.
37. Hart AJ, Whalen PJ, Shin LM, McNerney SC, Fischer H, Rauch SL. Differential response in the human amygdala to racial outgroup vs ingroup face stimuli. *Neuroreport*. 2000;11:2351-2355.
38. Phelps EA, O'Connor KJ, Cunningham WA, et al. Performance on indirect measures of race evaluation predicts amygdala activation. *J Cogn Neurosci*. 2000;12:729-738.
39. Canli T, Zhao Z, Brewer J, Gabrieli JD, Cahill L. Event-related activation in the human amygdala associates with later memory for individual emotional experience. *J Neurosci*. 2000;20:RC99.
40. Phan KL, Taylor SF, Welsh RC et al. Activation of the medial prefrontal cortex and extended amygdala by individual ratings of emotional arousal: a functional magnetic resonance imaging study. *Biol Psychiatry*. 2003;53:211-215.
41. Williams LM, Phillips ML, Brammer MJ, et al. Arousal dissociates amygdala and hippocampal fear responses: evidence from simultaneous fMRI and skin conductance recording. *Neuroimage*. 2001;14:1070-1079.
42. Taylor SF, Liberzon I, Koeppel RA. The effect of graded aversive stimuli on limbic and visual activation. *Neuropsychologia*. 2000;38:1415-1425.
43. Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR. The amygdala response to emotional stimuli: a comparison of faces and scenes. *Neuroimage*. 2002;17:317-323.
44. Hamann SB, Ely TD, Grafton ST, Kilts CD. Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nat Neurosci*. 1999;2:289-293.
45. Hamann SB, Ely TD, Hoffman JM, Kilts CD. Ecstasy and agony: activation of the human amygdala in positive and negative emotion. *Psychol Sci*. 2002;13:135-141.
46. Hamann S, Mao H. Positive and negative emotional verbal stimuli elicit activity in the left amygdala. *Neuroreport*. 2002;13:15-19.
47. Garavan H, Pendergrass JC, Ross TJ, Stein EA, Risinger RC. Amygdala response to both positively and negatively valenced stimuli. *Neuroreport*. 2001;12:2779-2783.
48. Liberzon I, Phan KL, Decker LR, Taylor SF. Extended amygdala and emotional salience: a PET activation study of positive and negative affect. *Neuropsychopharmacology*. 2003;28:726-733.
49. Anderson AK, Phelps EA. Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature*. 2001;411:305-309.
50. Phelps EA, O'Connor KJ, Gatenby JC, Gore JC, Grillon C, Davis M. Activation of the left amygdala to a cognitive representation of fear. *Nat Neuroscience*. 2001;4:437-441.
51. Killgore WD, Yurgelun-Todd DA. Sex differences in amygdala activation during the perception of facial affect. *Neuroreport*. 2001;12:2543-2547.
52. Morris JS, Ohman A, Dolan RJ. Conscious and unconscious emotional learning in the human amygdala. *Nature*. 1998;393:467-470.
53. Wright CI, Fischer H, Whalen PJ, McNerney SC, Shin LM, Rauch SL. Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *Neuroreport*. 2001;12:379-383.
54. Whalen PJ, Rauch SL, Etcoff NL, McNerney SC, Lee MB, Jenike MA. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci*. 1998;18:411-418.
55. Cahill L, Haier RJ, White NS, et al. Sex-related difference in amygdala activity during emotionally influenced memory storage. *Neurobiol Learn Mem*. 2001;75:1-9.
56. Gur RC, Mozley LH, Mozley PD, et al. Sex differences in regional cerebral glucose metabolism during a resting state. *Science*. 1995;267:528-531.
57. Cahill L. Neurobiological mechanisms of emotionally influenced, long-term memory. *Prog Brain Res*. 2000;126:29-37.
58. Taylor SF, Phan KL, Decker LR, Liberzon I. Subjective rating of emotionally salient stimuli modulates neural activity. *Neuroimage*. 2003;18:650-659.
59. Liberzon I, Taylor SF, Fig LM, Decker LR, Koeppel RA, Minoshima S. Limbic activation and psychophysiological responses to aversive visual stimuli. Interaction with cognitive task. *Neuropsychopharmacology*. 2000;23:508-516.
60. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *J Cogn Neurosci*. 2002;14:1215-1229.

61. Hariri AR, Bookheimer SY, Mazziotta JC. Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport*. 2000;11:43-48.
62. Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR. Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry*. 2003;53:494-501.
63. Lange K, Williams LM, Young AW, et al. Task instructions modulate neural responses to fearful facial expressions. *Biol Psychiatry*. 2003;53:226-232.
64. Morris JS, Ohman A, Dolan RJ. A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc Natl Acad Sci U S A*. 1999;96:1680-1685.
65. Keightley ML, Winocur G, Graham SJ, Mayberg HS, Hevenor SJ, Grady CL. An fMRI study investigating cognitive modulation of brain regions associated with emotional processing of visual stimuli. *Neuropsychologia*. 2003;41:585-596.
66. Pessoa L, McKenna M, Gutierrez E, Ungerleider LG. Neural processing of emotional faces requires attention. *Proc Natl Acad Sci U S A*. 2002;99:11458-11463.
67. Anderson AK, Christoff K, Panitz D, De Rosa E, Gabrieli JD. Neural correlates of the automatic processing of threat facial signals. *J Neurosci*. 2003;23:5627-5633.
68. Lane RD, Reiman EM, Bradley MM, et al. Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia*. 1997;35:1437-1444.
69. Lane RD, Reiman EM, Ahern GL, Schwartz GE, Davidson RJ. Neuroanatomical correlates of happiness, sadness, and disgust. *Am J Psychiatry*. 1997;154:926-933.
70. Reiman EM, Lane RD, Ahern GL, et al. Neuroanatomical correlates of externally and internally generated human emotion. *Am J Psychiatry*. 1997;154:918-925.
71. Drevets WC, Raichle ME. Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interactions between cognition and emotion. *Cognition and Emotion*. 1998;12:353-385.
72. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A*. 2001;98:4259-4264.
73. Johnson SC, Baxter LC, Wilder LS, Pipe JG, Heiserman JE, Prigatano GP. Neural correlates of self-reflection. *Brain*. 2002;125:1808-1814.
74. Kelley WM, Macrae CN, Wyland CL, Caglar S, Inati S, Heatherton TF. Finding the self? An event-related fMRI study. *J Cogn Neurosci*. 2002;14:785-794.
75. Zysset S, Huber O, Ferstl E, von Cramon DY. The anterior frontomedian cortex and evaluative judgment: an fMRI study. *Neuroimage*. 2002;15:983-991.
76. Mesulam MM. *Principles of Behavioral and Cognitive Neurology*. New York, NY: Oxford University Press; 2000.
77. Lane RD, Fink GR, Chau PM, Dolan RJ. Neural activation during selective attention to subjective emotional responses. *Neuroreport*. 1997;8:3969-3672.
78. Morgan MA, LeDoux JE. Contribution of ventrolateral prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Neurobiol Learn Mem*. 1999;72:244-251.
79. Abercrombie HC, Schaefer SM, Larson CL, et al. Metabolic rate in the right amygdala predicts negative affect in depressed patients. *Neuroreport*. 1998;9:3301-3307.
80. Liberzon I, Zubieta JK, Fig LM, Phan KL, Koeppe RA, Taylor SF. mu-Opioid receptors and limbic responses to aversive emotional stimuli. *Proc Natl Acad Sci U S A*. 2002;99:7084-7089.
81. Beauregard M, Levesque J, Bourgoin P. Neural correlates of conscious self-regulation of emotion. *J Neurosci*. 2001;21:RC165.
82. Teasdale JD, Howard RJ, Cox SG, et al. Functional MRI study of the cognitive generation of affect. *Am J Psychiatry*. 1999;156:209-215.
83. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain*. 1995;118(pt 1):279-306.
84. Whalen PJ, Bush G, McNally RJ, et al. The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol Psychiatry*. 1998;44:1219-1228.
85. Critchley HD, Elliott R, Mathias CJ, Dolan RJ. Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. *J Neurosci*. 2000;20:3033-3040.
86. Critchley HD, Mathias CJ, Dolan RJ. Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron*. 2001;29:537-545.
87. Lane RD, Reiman EM, Axelrod B, Yun LS, Holmes A, Schwartz GE. Neural correlates of levels of emotional awareness. Evidence of an interaction between emotion and attention in the anterior cingulate cortex. *J Cogn Neurosci*. 1998;10:525-535.
88. Lane RD, Chua PM, Dolan RJ. Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures. *Neuropsychologia*. 1999;37:989-997.
89. Mayberg HS, Liotti M, Brannan SK, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry*. 1999;156:675-682.
90. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiatry Clin Neurosci*. 1997;9:471-481.
91. Drevets WC, Price JL, Simpson JR Jr, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 1997;386:824-827.
92. Drevets WC, Ongur D, Price JL. Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. *Mol Psychiatry*. 1998;3:220-226.
93. Mayberg HS, Brannan SK, Mahurin RK, et al. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport*. 1997;8:1057-1061.
94. Cabeza R, Nyberg L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci*. 2000;12:1-47.
95. Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Brain Res Rev*. 1996;22:229-244.
96. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci*. 2002;3:655-666.
97. Schienle A, Stark R, Walter B, et al. The insula is not specifically involved in disgust processing: an fMRI study. *Neuroreport*. 2002;13:2023-2026.
98. Shin LM, Dougherty DD, Orr SP, et al. Activation of anterior paralimbic structures during guilt-related script-driven imagery. *Biol Psychiatry*. 2000;48:43-50.