

REVIEW

Functional Neuroanatomy of Emotion: A Meta-Analysis of Emotion Activation Studies in PET and fMRI¹

K. Luan Phan,^{*,2} Tor Wager,[†] Stephan F. Taylor,^{*} and Israel Liberzon^{*,‡}

**Department of Psychiatry and †Department of Psychology, University of Michigan, Ann Arbor, Michigan 48109; and ‡Psychiatry Service, Ann Arbor VAMC, Ann Arbor, Michigan 48105*

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Neuroimaging studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have begun to describe the functional neuroanatomy of 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, we sought to determine if common or segregated patterns of activations exist across various emotional tasks. We reviewed 55 PET and fMRI activation studies (yielding 761 individual peaks) which investigated emotion in healthy subjects. Peak activation coordinates were transformed into a standard space and plotted onto canonical 3-D brain renderings. We divided the brain into 20 non-overlapping regions, and characterized each region by its responsiveness across individual emotions (positive, negative, happiness, fear, anger, sadness, disgust), to different induction methods (visual, auditory, recall/imagery), and in emotional tasks with and without cognitive demand. Our review yielded the following summary observations: (1) The medial prefrontal cortex had a general role in emotional processing; (2) fear specifically engaged the amygdala; (3) sadness was associated with activity in the subcallosal cingulate; (4) emotional induction by visual stimuli activated the occipital cortex and the amygdala; (5) induction by emotional recall/imagery recruited the anterior cingulate and insula; (6) emotional tasks with cognitive demand also involved the anterior cingulate and insula. This review provides a critical comparison of findings across individual

studies and suggests that separate brain regions are involved in different aspects of emotion. © 2002 Elsevier Science (USA)

INTRODUCTION

It has long been proposed that emotion involves the limbic system (Papez, 1937; MacLean, 1952; LeDoux, 1996). Recently, this assumption has been tested with functional neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These studies have reported emotion-related increases in cerebral blood flow or BOLD signal (activations) in cortical, limbic, and paralimbic regions. Many authors have hypothesized that specific brain regions have specialized functions for emotional operations. For example, while some postulated that the amygdala is critical to fear-related processing (LeDoux, 2000), others have suggested that amygdala activations correspond to dispositional affective style (Irwin and Davidson, 1999). The medial prefrontal cortex has been hypothesized to have specific roles for emotional decision making (Damasio, 1996) and emotional self-regulation (Davidson, 2000), while the orbital prefrontal cortex is considered important for the evaluation of emotion-related reinforcement contingencies (Rolls, 1999). The retrosplenial cortex has been proposed as important in processing emotionally salient stimuli, particularly in the interaction between emotion and episodic memory (Maddock, 1999). In spite of general agreement about some of these specialized emotional regions, conflicting findings are often produced by studies using different induction methods and imaging techniques.

Taken separately, individual imaging studies cannot fully characterize which brain regions are responsible for emotion due to low statistical power and heterogeneity in task design, imaging methods, and analysis. These variations have made it difficult to interpret the

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² To whom correspondence and reprint requests should be addressed. Fax: (734) 647-8514. E-mail: luan@umich.edu.

differences in activation patterns found. Under this circumstance, a broader-based meta-analysis of multiple studies may be one solution (Fox *et al.*, 1998). By examining findings across studies, patterns of activations can be evaluated across similar and dissimilar emotional tasks. This meta-analysis examines findings across imaging studies in search of specific regions associated with emotional activation in general, with specific emotions and different induction methods. We also examined if there are brain regions associated with emotional activation tasks that had a cognitive component (e.g., emotional expression recognition, gender discrimination, etc.). Particularly, we examined how “sensitive” specific brain regions were to different emotional tasks (reflected by the percentage of studies reporting activation in a region according to a condition of interest). We also examined how “specific” certain brain regions were for different emotional responses (reflected by the frequency of activation in a specific region with a given task in comparison to other regions). The effect of gender and valence (the extent to which emotion is unpleasant or pleasant) on activation patterns, and the question of laterality in activation patterns are major topics in neuroimaging of emotion, and thus require an extensive and separate discussion. Therefore, we have chosen to report these results separately (Wager *et al.*, in preparation).

METHODS

Scope of Review

In order to illuminate both general and specific patterns of activation associated with different emotional tasks, we searched peer-reviewed journals (indexed in large databases [MEDLINE, PsychInfo, BrainMap]) for English-language manuscripts of PET and fMRI emotion induction studies published between January, 1990, and December, 2000. To allow us to performed planned meta-analysis, all reports included met the following criteria: (1) They involved unmedicated healthy adults; (2) They focused on higher-order mental processes of emotion (thus, studies of lower-order sensory or motor processes, such as gustatory/olfactory or pain induction, were excluded) [see reviews by by Small *et al.*, 1999; Casey *et al.*, 1994, respectively]; (3) They all measured regional cerebral blood flow (e.g., $O^{15}H_2O$ -PET) or blood oxygenation (e.g., BOLD-fMRI) across the entire brain (i.e., excluding studies that focused on limited regions of the brain); (4) They all used the image subtraction methodology to determine activation foci; (5) They provided standard Talairach (Talairach and Tournoux, 1988) or Montreal Neurologic Institute (MNI) coordinates, allowing for comparison of findings across different studies and different laboratories. We chose not to include studies on aversive and trace conditioning (Büchel *et al.*, 1998; Morris

et al., 1998b; LaBar *et al.*, 1998; Büchel *et al.*, 1999) because those tasks involve associative learning and behavioral conditioning (including acquisition and extinction), rendering them incomparable to the emotional tasks in our database. Furthermore, these fear-conditioning related activations were extensively discussed in a recent review by Büchel and Dolan (2000). Only activation peaks were examined in this meta-analysis. The reporting of deactivation or decreases in brain activity was not consistent across studies which did not allow meaningful generalization. Also, the neural mechanisms underlying reported deactivations remain undetermined and their interpretations remain inconclusive or unclear (Hutchinson *et al.*, 1999; Raichle *et al.*, 2001).

Organization of Results

Fifty-five publications/studies (43 PET and 12 fMRI) spanning from May, 1993, to December, 2000, that met our database criteria, yielding 119 subtractions/contrasts and 761 individual activation peaks, were included for meta-analysis (Table 1). Because the studies adopted different analysis methods and significance criteria, all foci were accepted when reported as significant by the criteria designated in the individual studies.

The activation results are grouped in the following manner: (1) Regions associated with Individual Emotion (fear, sadness, disgust, anger, happiness); (2) regions associated with Induction Method (visual, auditory, autobiographical recall/imagery); and (3) regions associated with presence and absence of Cognitive Demand. Table 1 lists all studies included in the review, arranged alphabetically, and identifies the Individual Emotion examined and the Induction Method employed. We examined the effect of Cognitive Demand, as a separate but related component of Induction Method, for a variety of reasons. Neuroimaging literature often distinguishes between cognitive and emotional tasks, but the majority of the emotional tasks contain various degrees of cognitive demand. Furthermore, there is a clear interaction between emotion and cognition on a functional level. To examine the neuroanatomic basis of this interaction, we examined the effect of these cognitive components in emotion activation by grouping conditions in which an emotional task was coupled with a concurrent cognitive task (e.g., gender/emotional expression discrimination, emotional rating, picture/face recognition/encoding, naming, counting, autobiographical recall/imagery, etc.) as Emotion + Cognition or *with* Cognitive Demand. Conversely, we grouped conditions in which the emotional task did not explicitly have a cognitive component (i.e., passive viewing, passive listening) as Emotion alone or *without* Cognitive Demand. This classification allows us to examine the effect of a “nonemotional” cognitive component on emotional tasks.

TABLE 1

List of Emotion Activation Studies Included in the Meta-Analysis

Study No.	Reference	Induction Method			Type of Emotion				
		Visual	Auditory	Recall	Happy	Fear	Anger	Sad	Disgust
1	Baker 97		X		X			X	
2	Beauregard 97	X							
3	Beauregard 98	X						X	
4	Blair 99	X					X	X	
5	Blood 99		X						
6	Breiter 96	X			X	X			
7	Canli 98	X							
8	Crosson 99		X						
9	Damasio 00			X	X	X	X	X	
10	Dolan 00	X							
11	Dougherty 99			X			X		
12	Frey 00		X						
13	Gemar 96			X				X	
14	George 93	X							
15	George 94	X						X	
16	George 95			X	X			X	
17	George 96a		X						
18	George 96b			X	X			X	
19	Hamann 99	X							
20	Hariri 00	X							
21	Isenberg 99	X				X			
22	Kimbrell 99			X		X	X		
23	Kosslyn 96	X							
24	Lane 97a	X							
25	Lane 97b	X							
26	Lane 97c	X		X	X			X	X
27	Lane 98	X		X					
28	Lane 99	X							
29	Liberzon 00	X							
30	Liotti 00			X		X		X	
31	Maddock 97		X			X			
32	Mayberg 99			X				X	
33	Morris 96	X			X	X			
34	Morris 98a	X			X	X			
35	Morris 99		X			X			
36	Nakamura 99	X							
37	Paradiso 97	X			X	X			X
38	Paradiso 99	X							
39	Pardo 93			X				X	
40	Partiot 95			X				X	
41	Phillips 97	X				X			X
42	Phillips 98a	X	X			X			X
43	Phillips 98b	X			X			X	
44	Pietrini 00			X					
45	Rauch 99			X					
46	Redoute 00	X							
47	Reiman 97	X		X					
48	Royet 00	X	X						
49	Shin 00			X					
50	Simpson 00	X							
51	Sprengelmeyer 98	X				X	X		X
52	Taylor 98	X							
53	Taylor 00	X							
54	Teasdale 99	X							
55	Whalen 98b	X							

The standard coordinates of activation peaks reported by individual studies were plotted onto lateral and medial views of a 3-D canonical brain image (SPM

96, Wellcome Department of Cognitive Neurology, London; derived from the MNI brain template). Figures 1A–1C show the result of grouping plotted activa-

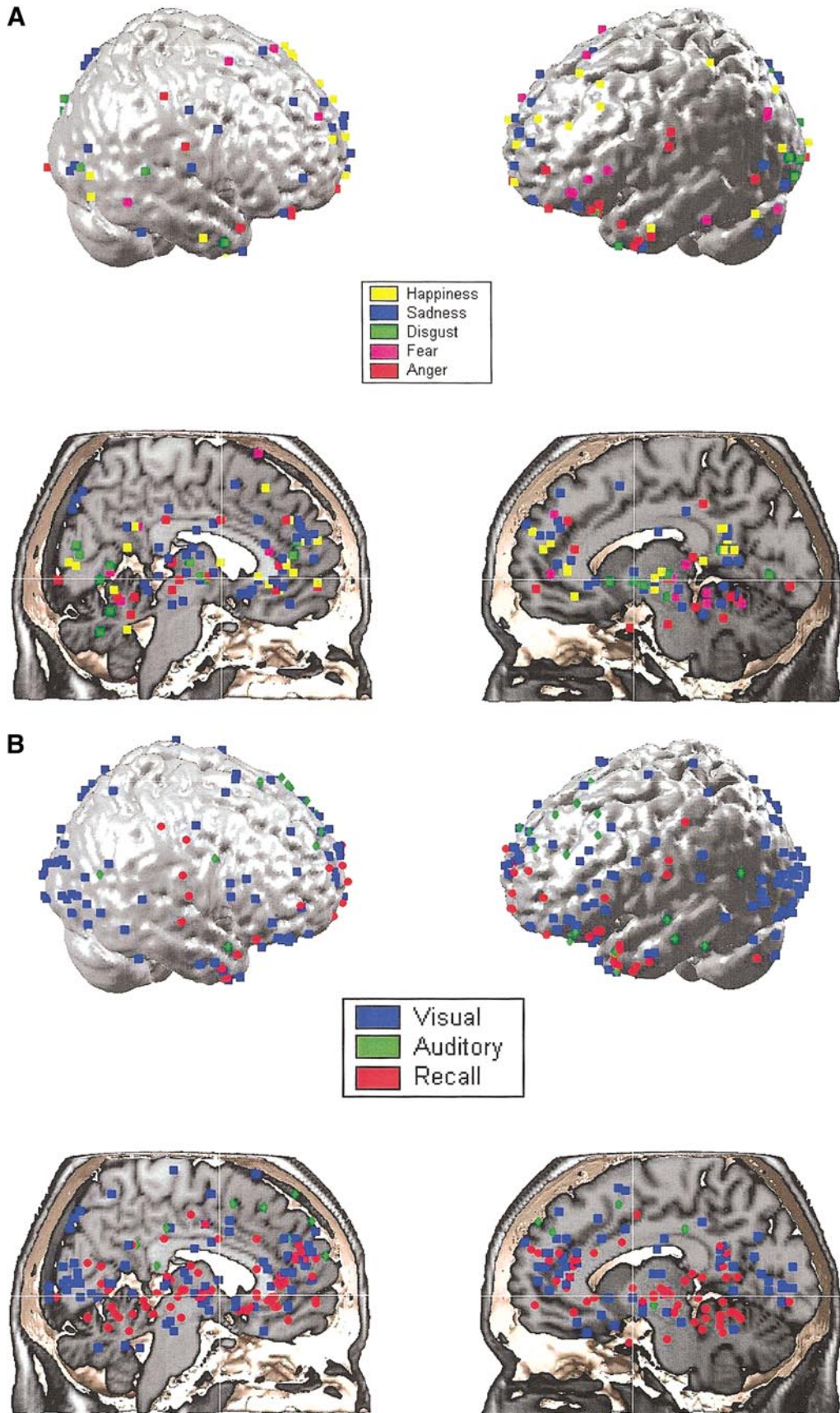


FIG. 1A. Activation foci: Individual emotion.
FIG. 1B. Activation foci: Induction method.

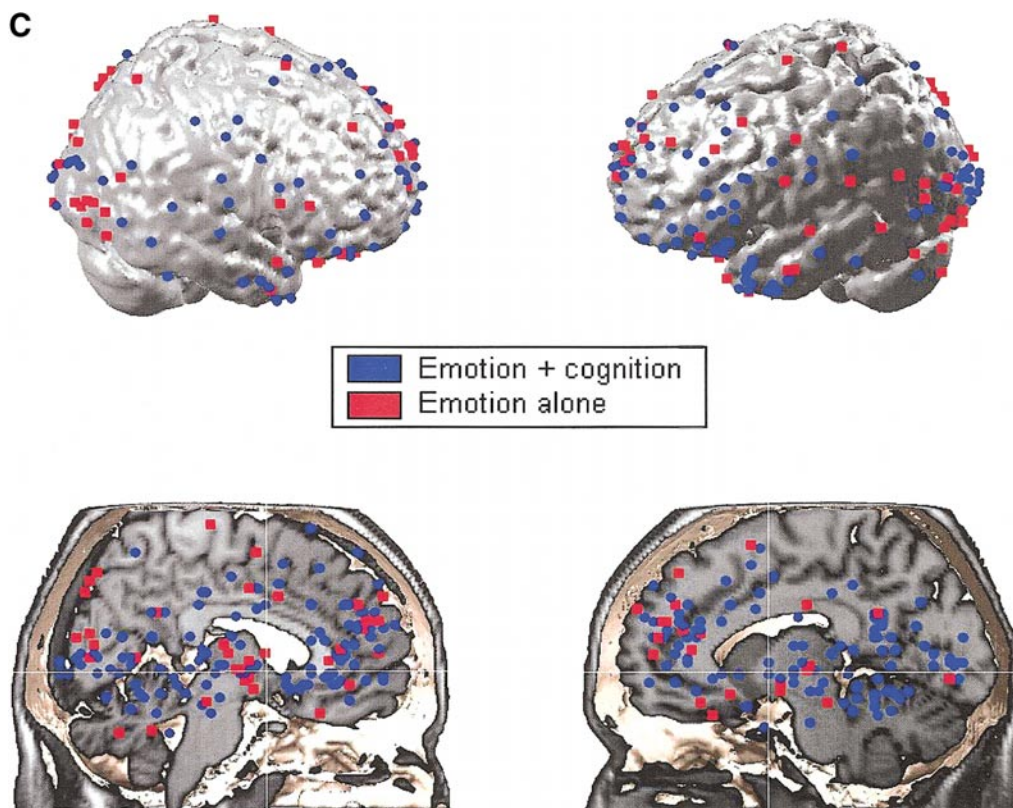


FIG. 1C. Activation foci: Cognitive demand.

tion foci according to Individual Emotion, Induction Method, and Cognitive Demand. In order to make direct comparisons across studies, we translated reported Talairach coordinates (Talairach and Tournoux, 1998) into MNI coordinates (transformation developed by Matthew Brett, <http://www.mrc.cbu.cam.ac.uk/Imaging>). Because differences in image smoothing techniques can lead to different numbers of activation foci, we chose not to include spatial extent of activation peaks when plotting onto the 3-D canonical brain.

For a semiquantitative analysis, we divided the atlas brain into 20 general regions, and examined whether activations in each specific region was associated with different Individual Emotion, Induction Method, and Cognitive Demand. Each study included in this review identified the location of the activation peak as anatomical structure/gyrus and/or Brodmann area. We used this information to localize the activation peaks in the 20 brain regions used in this review. The number of activation peaks reported for a single region differed according to each study's chosen statistical threshold and analysis methods. Therefore, we considered a region as activated for a particular study if one or more activation peak in this region was reported. This approach was chosen to counterbalance the tendency for overestimating activations based on variable thresholds used in different studies, and allowed us to esti-

mate the percentage of studies that reported an activation foci in a specific region in response to each Individual Emotion, Induction Method, and Cognitive Demand (Figs. 2A–2C).

Additionally, we examined how specific the reported regional activations were to Individual Emotion, Induction Method, and Cognitive Demand. For all studies that employed similar contrasts and methods, we compared the number of studies that found activation in a particular region to those that did not using chi-square (X^2) analysis. The results of the X^2 analysis are presented in Fig. 2.

RESULTS AND DISCUSSION

1. Regions Involved Across Individual Emotions

1.1. General emotional processing and the medial prefrontal cortex. No specific brain region was consistently activated in the majority of studies, across individual emotions and induction methods, suggesting that no single brain region is commonly activated by all emotional tasks. Although no region was activated in over 50% of all studies, we did find that the medial prefrontal cortex (MPFC) was commonly activated, and that its activation was not specific to a specific emotion or induction method (see Figs. 2A and 2B).

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 that certain aspects may be shared across different emotional tasks. Figure 2A shows that the MPFC was activated across multiple individual emotions (four of five specific emotions in at least 40% of studies). Accordingly, X^2 analysis revealed no specific association between the MPFC and Individual Emotion as compared to other regions. These findings suggest that the MPFC may have a general role in emotional processing, as suggested by Lane, Reiman, and colleagues, 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 (Lane *et al.*, 1997a; Lane *et al.*, 1997c; Reiman *et al.*, 1997). This is consistent with the notion that a number of processes are potentially common to various emotional tasks (e.g., appraisal/evaluation of emotion, emotional regulation, and emotion-driven decision-making). Lane *et al.* (1997b) did find that the MPFC (BA9) activated when subjects internally-attended to their emotional state, but not when they externally attended to nonaffective characteristics of a picture stimulus. Furthermore, activity in the MPFC 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 (Lane *et al.*, 1998). One possibility therefore is that the MPFC may be involved in the cognitive aspects (e.g., attention to emotion, appraisal/identification of emotion) of emotional processing (Drevets and Raichle, 1998).

Given the putative importance of cognition in emotion, we questioned whether the MPFC can be subdivided into affective and cognitive regions, which has been observed in the anterior cingulate cortex (ACC) (Bush *et al.*, 2000). The ACC is known to be involved in a form of attention that serves to regulate both cognitive and emotional processing (Whalen *et al.*, 1998a; Bush *et al.*, 2000), and is closely interconnected to the MPFC (Petrides and Pandya, 1999; Devinsky *et al.*, 1995). Figures 1A and 1B show that activations reported in the prefrontal cortex in response to different Individual Emotions and Induction Methods are located within ventral-rostral BA 9 and 10 of MPFC, and extend into the affective division of rostral anterior cingulate cortex (ACCad) (BA rostral 24, anterior/ventral 32, 33). While the activations located in the area of the MPFC are more ventral and less dorsal, we did not find any evidence for a functional affective-cognitive division of the MPFC. Our Cognitive Demand analysis revealed that relatively much fewer *Emotion alone* peaks fell into dorsal MPFC (see Fig. 1C), in comparison to studies with tasks that involved *Emotion and Cognition*. Thus, MPFC appears equally sensitive to

both emotional tasks with and without Cognitive Demand, as activations from both conditions cluster in ventral MPFC (see Figs. 1C and 2C). Interestingly, previous meta-analyses of cognition revealed that the rostral-ventral and orbital regions of the MPFC are largely insensitive to cognitive tasks (Duncan and Owen, 2000; Cabeza and Nyberg, 2000).

2. Regions Associated with Individual Emotions

2.1 Fear and the amygdala. Specifically, fear induction had a strong association with the amygdala. Sixty percent of studies that examined fear activated the amygdala ($X^2 = 12.57$, $P = 0.01$) (Fig. 2A). Several lines of evidence support the notion that the amygdala is responsible for detecting, generating, and maintaining fear-related emotions. Particularly, the amygdala has been implicated in the recognition of fearful facial expressions (Adolphs *et al.*, 1995; Calder *et al.*, 1996), feelings of fear after procaine induction (Ketter *et al.*, 1996), fear conditioning (LeDoux, 1993; Bechara *et al.*, 1995; LaBar *et al.*, 1995; Morris *et al.*, 1998b; Whalen *et al.*, 1998b), and in evocation of fearful emotional responses from direct stimulation (Halgren *et al.*, 1978). The amygdala also appears important in the detection of environment threat (Scott *et al.*, 1997; Isenberg *et al.*, 1999; Phillips *et al.*, 1998a), as well as in the coordination of appropriate responses to threat and danger (Kluber and Bucy, 1939; Weiskrantz, 1956; King, 1992). Strikingly, of the eight studies that examined cerebral responses to fearful faces, six pointed to the critical involvement of the amygdala (Morris *et al.*, 1996; Breiter *et al.*, 1996; Phillips *et al.*, 1997; Phillips *et al.*, 1998a; Morris *et al.*, 1998a; Whalen *et al.*, 1998a). Fear-associated amygdalar activations also extended into other modalities such as words (Isenberg *et al.*, 1999) and vocalizations (Phillips 1998a). Morris *et al.* (1996) found that the amygdalar response to fearful faces showed a significant interaction with the intensity of emotion (increasing with increasing fearfulness) and that 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 (Morris *et al.*, 1998b; Whalen *et al.*, 1998a).

Given that fear is 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 (Davis and Whalen, 2001). Whalen *et al.* (1998b) observed that the amygdala responds to fearful faces despite the lack of explicit rec-

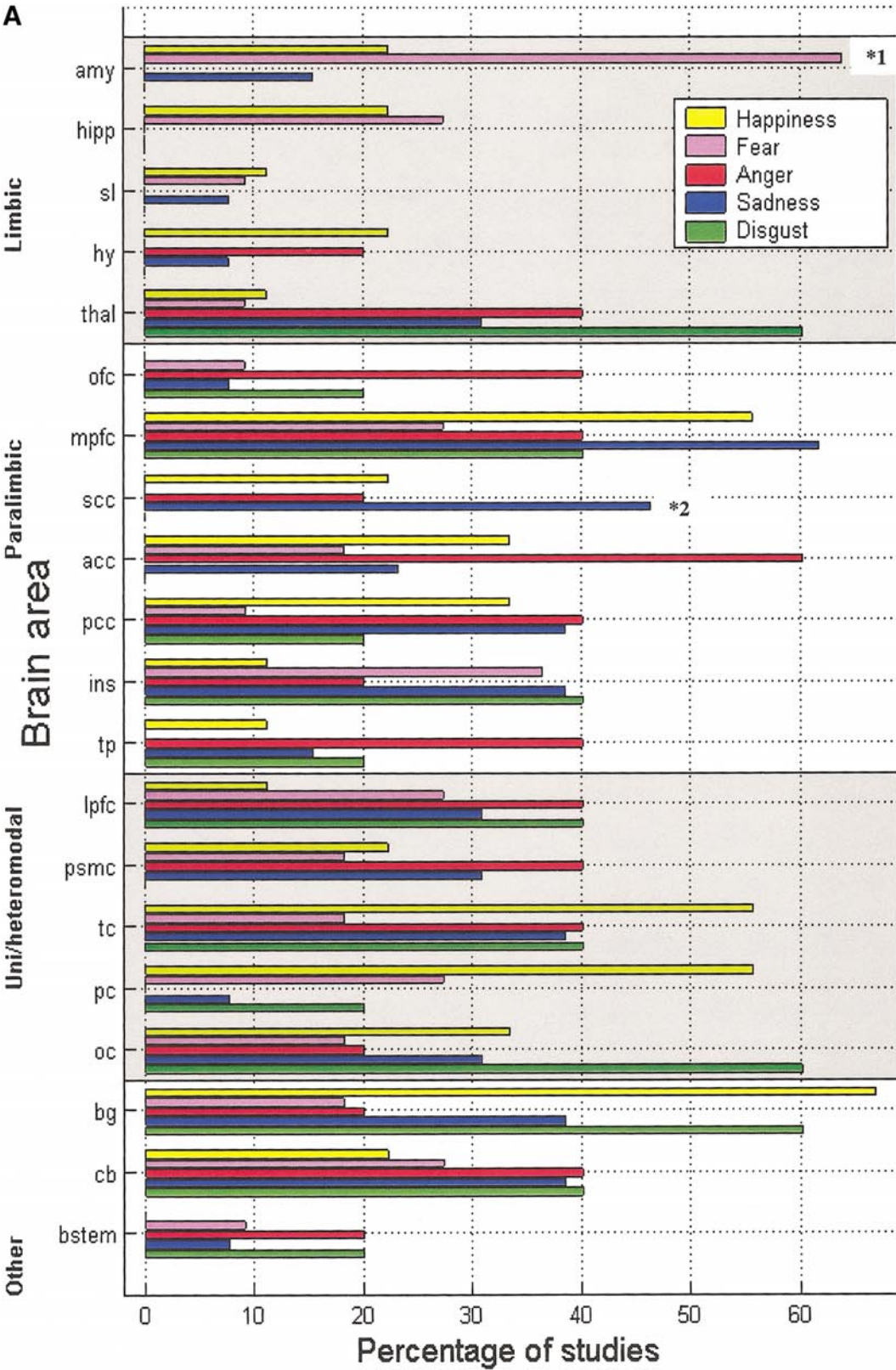
ognition of the expression and that fearful faces are more likely to signify a signal for threat than to induce fear given that subjects often do not report being afraid. Hence, the amygdalar activations may be primarily for processing affective information in service of imparting danger warnings. Amygdala activations occur throughout various evocative stimuli, including fear faces (Morris *et al.*, 1996; Breiter *et al.*, 1996; Phillips *et al.*, 1997), aversive pictures (Irwin *et al.*, 1996; Taylor *et al.*, 1998; Simpson *et al.*, 2000), as well as sad (Blair *et al.*, 1999) and happy faces (Breiter *et al.*, 1996), and positive pictures (Hamann *et al.*, 1999). A positive correlation of blood flow in the amygdala was found with subsequent recall of pleasant pictures (Hamann *et al.*, 1999): in that study, the amygdala activated to both pleasant and unpleasant pictures. Thus, the amygdala may not exclusively respond to affectively laden stimuli, but may respond to meaningful stimuli in general. Our own findings also concur this interpretation since we have observed that amygdala also responds to nonaversive/neutral (Taylor *et al.*, 2000) and positive (Liberzon *et al.*, submitted) pictures, supporting evidence from animal studies of the structure's role in mediating conditioned responses which enhance information processing to nonaversive stimuli (Everitt, 1991). These findings suggest that the amygdala responds to emotional importance or stimulus salience, regardless of valence (whether the content is pleasant or aversive/unpleasant). This is also consistent with psychophysiologic evidence of skin conductance response (SCR) to affective pictures which demonstrate a response to salient, arousing stimuli, regardless of emotional valence (Lang *et al.*, 1993).

2.2 Sadness and the subcallosal cingulate. Sadness induction was significantly associated with subcallosal cingulate cortex (SCC) activation. About 46% of sadness induction studies reported activation of the SCC, region localized to the ventral/subgenual anterior cingulate (BA 25), over twice as frequently as any other specific emotion ($X^2 = 9.24$, $P = 0.05$). Interestingly, hypometabolism or hypoperfusion has been found in the SCC in resting state studies of patients with clinical depression, a mood disorder with relatively more sustained sadness (Baxter *et al.*, 1985; Mayberg, 1994; Drevets *et al.*, 1997). As expected, activity in the subgenual cingulate (BA 25) increased when depressed subjects respond to pharmacologic treatment (Brody *et al.*, 1999; Mayberg *et al.*, 2000). George *et al.* (1995) speculated that dysphoria-induced hyperactivity in this area may lead those susceptible towards a compensatory pattern of hypometabolism. Because Reiman and colleagues (1997) found anterior cingulate activity to recall-generated but not film-induced sadness, they interpreted that the SCC activations may result more from the cognitive process of internally generating emotion, and less from sadness itself.

Though this review found that many of the SCC activations arose from studies in which sadness was transiently induced by autobiographical scripts (George *et al.*, 1995; Lane *et al.*, 1997c; Mayberg *et al.*, 1999; Liotti *et al.*, 2000), the X^2 analysis did not support the notion that SCC activation was specifically associated with recall induction, as compared to other induction methods. The inconsistent findings in earlier activation studies on transient sadness in healthy subjects, particularly in the subgenual ACC (Gemar *et al.*, 1996; Pardo *et al.*, 1993; George *et al.*, 1995), may be attributed to the differences in provocation method. Particularly, subjects were partly or fully scanned while they were actively generating the targeted emotional state with additional cognitive tasks such as recalling or visualizing emotional memories. Liotti *et al.* (2000) and Mayberg *et al.* (1999) attempted to address these perceptual or cognitive confounds by scanning subjects after they had achieved a desired intensity of sadness, and confirmed the activations in subgenual ACC (BA 25).

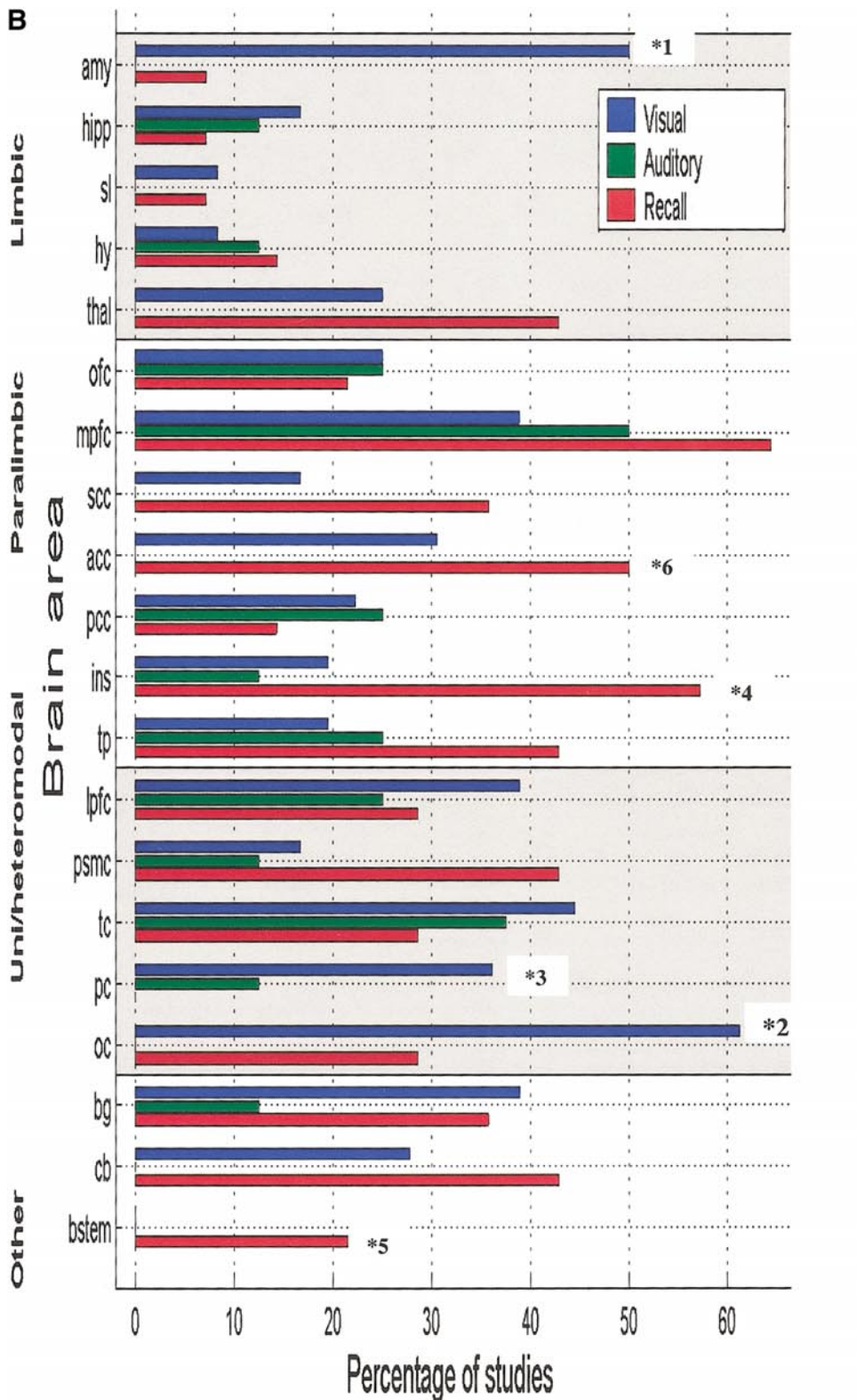
2.3 Happiness and the basal ganglia. Nearly 70% happiness induction studies reported activation in the basal ganglia (BG) (Fig. 2A). The notion that this area may be important in positive emotions, such as happiness, gains support from multiple in vivo investigations of addictive substances and behaviors (Breiter *et al.*, 1997; Stein *et al.*, 1998; Koob, 1992; Koch *et al.*, 1996), reward processing (Rolls, 1999), and enjoyable (playing a video game) activities (Koepp *et al.*, 1998). Activations in the basal ganglia, including the ventral striatum and putamen, have been observed in response to happy faces (Whalen *et al.*, 1998a; Morris *et al.*, 1996, 1998a; Phillips *et al.*, 1998b), pleasant pictures (Lane *et al.*, 1997a; Lane *et al.*, 1999; Davidson and Irwin, 1999), happiness-induced recall (George *et al.*, 1996b; Damasio *et al.*, 2000), pleasant sexual and successful competitive arousal (Rauch *et al.*, 1999; Redoute *et al.*, 2000). Given its rich innervation of mesolimbic dopaminergic neurons, the basal ganglia/ventral striatum is well positioned to respond to incentive reward motivation and to pregoal attainment of positive affect arising from progression toward a desired goal (Davidson and Irwin, 1999), consistent with the notion that happiness can be conceptualized as an approach emotion (Davidson *et al.*, 1990).

2.4 Disgust and the basal ganglia. Interesting, we also found that disgust induction frequently activated the BG; 60% of studies evoking disgust reported engagement of the BG (Fig. 2A). Contrary to happiness, disgust has been theoretically conceptualized as a withdrawal emotion (Davidson *et al.*, 1990). The reviewed studies suggest that, particularly, facial expressions of disgust activated the BG (Phillips *et al.*, 1997, 1998a; Sprengelmeyer *et al.*, 1998). Sprengelmeyer and colleagues (1998) hypothesized a specific



*1 $\chi^2 = 12.57$, $p = .01$, Cramer's $V = 0.54$
*2 $\chi^2 = 9.24$, $p = .05$, Cramer's $V = 0.46$

FIG. 2A. Regional activations: Individual emotions.



*1 $\chi^2 = 12.93$, $p = .002$, Cramer's $V = 0.47$

*2 $\chi^2 = 11.86$, $p = .003$, Cramer's $V = 0.45$

*3 $\chi^2 = 7.86$, $p = .02$, Cramer's $V = 0.37$

*4 $\chi^2 = 8.23$, $p = .02$, Cramer's $V = 0.38$

*5 $\chi^2 = 6.51$, $p = .04$, Cramer's $V = 0.34$

*6 $\chi^2 = 5.96$, $p = .05$, Cramer's $V = 0.32$

FIG. 2B. Regional activations: Induction method.

functional role for the basal ganglia in processing disgust, consistent with observations that patients with Huntington's disease and obsessive-compulsive disorder, who have neuropathology in their basal ganglia, have impairments in recognizing facial expressions of disgust compared to other emotions. The activations seen in the basal ganglia in response to disgust may represent a state of preparedness triggered by a warning stimulus to process emotionally salient information (Sprengelmeyer *et al.*, 1998). With its known motor functions, the basal ganglia may also serve to coordinate appropriate action responses to stimuli that unpleasant (inducing disgusting), or pleasing (promoting happiness), in nature, and guide the organism towards a desired goal (e.g., to approach or withdraw) (Panksepp, 1998).

3. Regions Associated with Induction Method

3.1 Regions involved in emotion induction with and without cognitive demand. This meta-analysis found that emotional tasks with cognitive components specifically engaged the ACC as compared to passive emotional conditions (36 vs 12%, respectively; $X^2 = 3.52$, $P = 0.06$). Earlier, when discussing the findings of the MPFC activation with both Emotion + Cognition and Emotion alone tasks, we hypothesized that activations seen in the MPFC are driven by the general component of the emotional task (e.g., with little impact by Cognitive Demand), and interpreted that the MPFC may have a general role in emotional processing. We speculated that the MPFC may respond to cognitive aspects that are potentially common across various emotional responses (e.g., attention to emotion, appraisal or interpretation of emotion), which are implicit to the emotional tasks and therefore are present both in the studies with Cognitive Demand and in the studies with Emotion alone. However, based on this analysis, when the cognitive components are explicit to an emotional task (e.g., gender identification, recognition/encoding or rating of emotional stimuli, biographical recall of emotion) rendering these task in the "with Cognitive Demand" category, it appears that the ACC is recruited. Therefore, the ACCad may interact with the MPFC to regulate interconnected cognitive and emotional tasks, depending on whether the cognitive component is implicit or explicit to that emotional response. Together, the rostral ACC and MPFC, with extensive connections to subcortical limbic structures, constitute both the heteromodal association cortex and paralimbic cortex respectively, and therefore comprise a plausible transition and interaction zone between affective and cognitive processing.

The MPFC and ACCad may also have additional emotional modulatory functions from this cognitive-emotion interaction. As noted above, conditions with and without Cognitive Demand equally activate the

MPFC, while cognitively-bound emotional tasks specifically engaged ACC. While most Individual Emotions activate both the MPFC and ACC, one exception involves fear, which recruits this region at frequencies fewer than 30% and 20% respectively (see Fig. 2B). Instead, fear studies engage the amygdala robustly (over 60% frequency; discussed earlier). Additionally, passive emotional conditions without Cognitive Demand (e.g., Emotion alone) activate the amygdala more often than cognitive emotional tasks. Given their putative affective-cognitive functions and reciprocal connections to subcortical limbic structures, the MPFC and ACC could serve as top-down modulators of intense emotional responses, especially those generated by the amygdala. Several lines of evidence support such an interpretation. From animal studies, the amygdala has been shown to be critical in fear conditioning (LeDoux, 1994). However, one can prolong the extinction of this conditioned fear by ablation of the MPFC (Morgan *et al.*, 1993). Lesions in the human rostral MPFC also lead to socially inappropriate expressions of emotions and impairments in making advantageous personally relevant decisions (Damasio, 1994), suggesting a lack of cognitive processing of emotionally "loaded" situations. Furthermore, glucose metabolism in the MPFC is strongly inversely associated with the glucose metabolic rate of the amygdala (Ambercrombie *et al.*, 1996). Our group 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) (Taylor *et al.*, submitted). Additionally, deactivation of the amygdala has been observed in several tasks that involve higher cognitive processing (Drevets and Raichle, 1998). One alternative hypothesis of these reciprocal findings is that limbic structures, like the amygdala, are more likely to respond 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 (Reiman *et al.*, 1997; Teasdale *et al.*, 1999).

3.2 Recall induction and the anterior cingulate. Similar to conditions with Cognitive Demand, those which induced emotions by evoking memories or imagery of personally relevant affectively laden events required 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 induction studies, respectively ($X^2 = 5.96$, $P = 0.05$). As described above, recruitment of the ACC was specific to cognitively demanding emotional tasks, and therefore, this association suggests that recalled emotions are cognitively elicited, as noted by Reiman *et al.* (1997) and

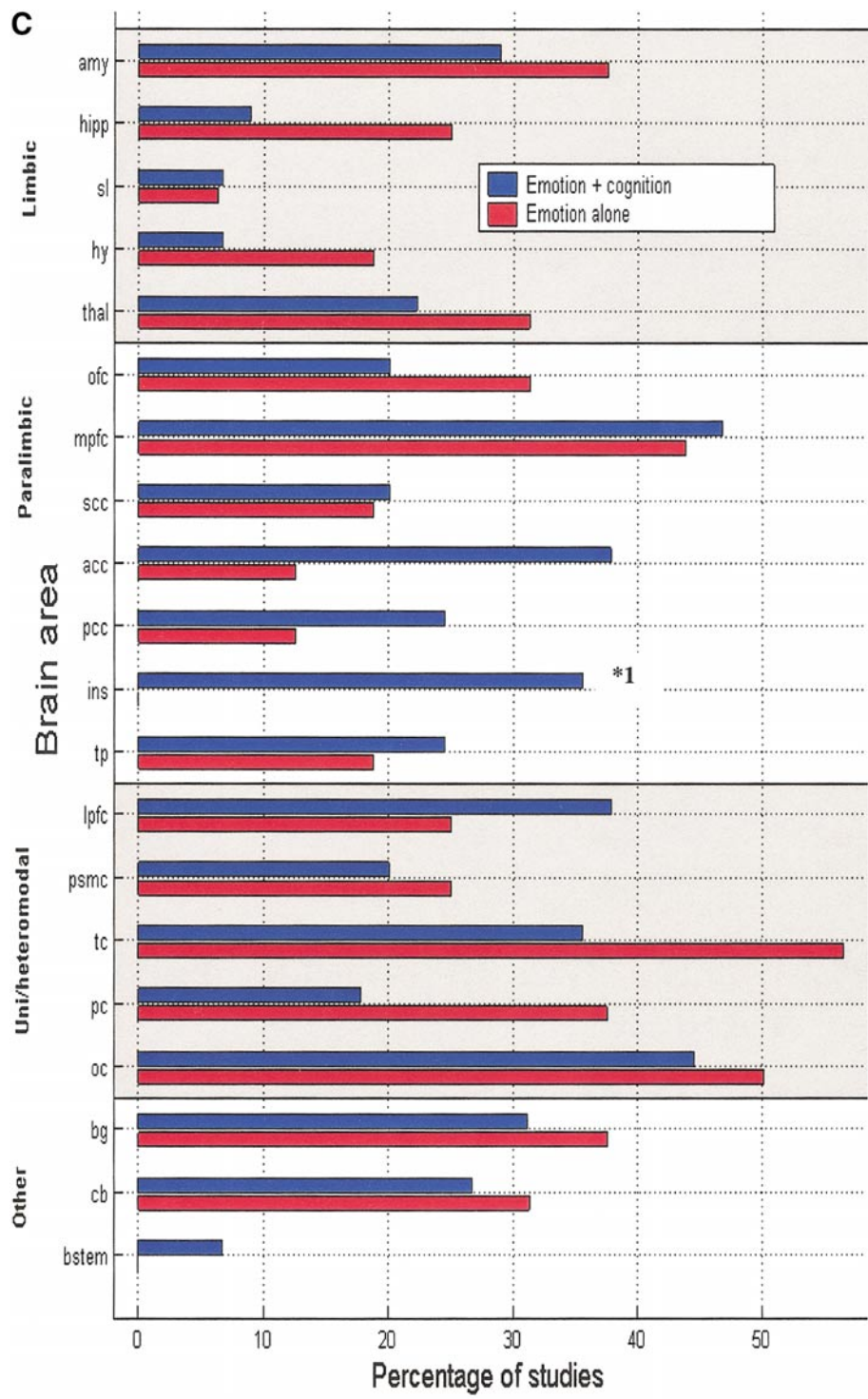
Teasdale *et al.* (1999). Given its known cognitive functions including modulation of attention and executive functions, and interconnections with subcortical limbic structures, the ACC's involvement in cognitive induction of emotional response, is not surprising. Such a process demands cognitive effort, as subjects are instructed to recall or imagine an emotionally laden personal event then self-induce or internally generate intense target emotions (Teasdale *et al.*, 1999). Moreover, the ACC is consistently activated in semantic and episodic memory retrieval tasks (Cabeza and Nyberg, 2000).

3.3 Recall induction, cognitive demand, and the insula. Nearly 60% of recall induction studies reported activation of the insula, compared to less than 20% of either visual or auditory inductions ($X^2 = 8.23$, $P = 0.02$). Like the ACC, recruitment of the insula was also identified more with cognitively demanding emotional tasks ($X^2 = 7.71$, $P = 0.01$), than with passive emotional tasks. Lane *et al.* (1997c) and Reiman *et al.* (1997) specifically found that emotional recall, but not emotional film viewing, engaged the insula. Our findings as well as earlier studies on non-human primates (Augustine *et al.*, 1996) support the suggestion that the insula is preferentially involved in the evaluative, experiential, or expressive aspects of internally generated emotions (Reiman *et al.*, 1997). In a study in which multiple specific individual emotions were induced by recall (happiness, sadness, fear, and disgust), Damasio and colleagues (2000) found that all emotions engaged the cingulate, insular cortex, and brainstem. Their findings are consistent with anatomic evidence that these regions are direct and indirect recipients of signals from the internal milieu and viscera, which are important in the regulation of homeostasis. Given this proposed role of emotion in maintaining homeostasis, Damasio *et al.* (2000) suggest that these regions, while engaged in the recall and self-generation of affect, monitor the ongoing internal emotional state of the organism, and may represent the neural correlates of mental states known as feelings. Reiman *et al.* (1997) had posited that the insula may participate in the evaluation of "distressing cognitions, interoceptive emotional significance" as an alarm center for internally-sensed dangers or homeostatic changes. Such an internal alarm hypothesis is consistent with our findings that the insula is associated with both self-induced or internally generated recalled emotions and with cognitively demanding tasks.

3.4 Visual induction and the occipital cortex. The occipital/visual cortex (OC) (mainly BA 18 and 19, but also occipital gyrus and fusiform gyrus) was almost exclusively activated by visually evocative stimuli. Of the 35 visual induction studies, 60% reported activation in the OC, which were reported in only 29% and 0% of recall and auditory induction studies, respec-

tively. As a general rule, the studies included in this review controlled for activations driven by simple sensory processing by designing both the target and control conditions to have similar sensory loads (e.g., conditions with emotionally laden visual stimuli were compared with conditions with emotionally neutral visual stimuli). Often, the pictorial stimuli were matched for color, luminance, and complexity across target and control conditions. The visual stimuli that activated OC were diverse and included pleasant and aversive pictures (Kosslyn *et al.*, 1996; Lane *et al.*, 1997a; Lang *et al.*, 1998; Reiman *et al.*, 1997; Taylor *et al.*, 1998, 2000; Lane *et al.*, 1999; Paradiso *et al.*, 1999; Simpson *et al.*, 2000; Kalin *et al.*, 1997; Irwin *et al.*, 1997), emotional faces (Morris *et al.*, 1998a; Sprengelmeyer *et al.*, 1998), and emotional films (Paradiso *et al.*, 1997; Lane *et al.*, 1997c; Beauregard *et al.* 1998). The modulation of the OC by the emotional components of visual induction may have been driven by either (1) from the processing of emotionally loaded content or, (2) from an interaction between visual perception and emotional processing.

Due to its engagement across multiple visual emotion tasks, it has been proposed that the OC mediates and appraises visually relevant, complex emotional stimuli (Lane *et al.*, 1997a; Beauregard *et al.*, 1998). Reiman and colleagues (1997) suggested that visual association areas in occipitotemporal cortex could be involved in the evaluation procedure of complex visual stimuli with emotional relevance. The activations in the visual cortex were found to be independent of the type of emotions by a number of authors (Kosslyn *et al.*, 1996; Lane *et al.*, 1997; Lang *et al.*, 1998; Reiman *et al.*, 1997). An alternative interpretation is that the occipital cortex is recruited because the visual stimuli are highly arousing, as such stimuli appears to activated perceptual areas more extensively (Lang *et al.*, 1998; Taylor *et al.*, 2000). Differences in image complexity, particularly semantic complexity, has been proposed as the underlying mediator of the occipital cortex activations despite experimentally balancing for the content of images for luminance, color, and detail (Irwin *et al.*, 1997; Taylor *et al.*, 2000). For example, visual cortex activation may also be attributed to differential eye movements between emotional and non-emotional stimuli due to complexity. However, Lang *et al.* (1998) demonstrated no difference in the duration or magnitude of scanning eye movements between the stimuli, and Lorge *et al.* (2000; unpublished data) reported that the extent of eye movements did not correlate with occipital cortex responses. Another possible contribution to the activation found in the visual cortex, particularly in the fusiform gyrus, may arise from the presence of faces in the pictorial and film stimuli. However, Simpson *et al.* (2000) found that the OC activation in their study was related to the emotional valence of the pictures not the presence of faces, and suggested



*1 $\chi^2 = 7.71, p = .01, \text{Cramer's } V = 0.36$

FIG. 2C. Regional activations: Cognitive demand.

that the presence of faces could not fully explain the visual cortex/fusiform activations. Additional studies specifically examining the effect of image content will

be needed to completely rule out potential confounding activations due to visual complexity and/or arousal. One plausible explanation is that visual processing

areas may represent top-down modulatory effects on the visual processing stream, particularly in relation to the amygdala, which was also found to be specific to visual induction. Anatomically, projections from limbic regions like the amygdala extend to all the processing steps in the ventral visual stream, including the primary visual cortex (Amaral *et al.*, 1984). A component of this top-down processing may be the selective attention that drives the modulation of visual processing (Corbetta *et al.*, 1993). Anatomical studies has shown that the primate amygdala receives substantial input from temporal visual-association areas (Iwai *et al.*, 1987, Aggleton *et al.*, 1980). Both Morris *et al.* (1998a) and Sprengelmeyer *et al.* (1998) proposed a neuro-modulatory function (top-down processing) of the amygdala on extrastriate cortical regions after finding an inverse correlation of amygdala and fusiform activity in response to fearful faces. Morris *et al.* (1998) hypothesized that extrastriate regions have functional interactions with the amygdala, evidenced by other facial emotion processing studies (George *et al.*, 1993; Adolphs *et al.*, 1996).

3.5 Visual induction and the amygdala. The visual induction method also preferentially activated the amygdala, over recall and auditory-generated emotion. Fifty percent of visual induction studies reported activation of the amygdala, compared to 7% and 0% of recall and auditory inductions, respectively ($X^2 = 12.93$, $P = 0.002$). From this, one can propose that the amygdala has a specialized role in processing visually relevant emotional cues, signalling fear, aversiveness, or salience. Because of its projections to virtually all levels of visual processing in the occipital cortex, the amygdala is positioned to modulate visual input, based on emotional significance, at a variety of levels along this visual processing stream. Hence, as discussed earlier, the amygdalar activations may be primarily for processing affective information within the visual processing stream in service of imparting danger warnings (Davis and Whalen, 2001). Similarly, others have suggested that the amygdalar response to visual emotionally stimuli may be in the serviced of assigning emotional significance to sensory, particularly visual, inputs (Simpson *et al.*, 2000) or that because of its modulatory influences, the amygdala may facilitate processing of salient, adaptively significant visual inputs (Morris *et al.*, 1998). Given that humans rely on vision, more than hearing or olfaction, to evaluate changes in the environment, the amygdala is well positioned to alert us to visual threat following perception by the occipital cortex.

Interestingly, very few recall-driven emotion activation studies engaged the amygdala (at 7% frequency). Some authors have hypothesized that the amygdala is less engaged by recalled emotions than for visually-evocative emotions (Reiman *et al.*, 1997; Damasio *et al.*,

2000). Thus, the amygdala may be more responsible for processing of externally-cued perceptual emotional stimuli (Reiman *et al.*, 1997; Teasdale 1999), and less involved in internally generated recollection or imagery of those stimuli (Reiman *et al.*, 1997; Whalen *et al.*, 1998; Rauch *et al.*, 1999; Shin *et al.*, 2000; Damasio *et al.*, 2000). Another potential issue is that many memories recalled are likely to involve more than one emotion (George *et al.*, 1995), and thereby may reduce statistical power to detect subtle changes in the amygdalar response, which may also be selective for certain emotions. The relationship of self-generated emotion by recalling personal events in a controlled environment like a PET scanner is clearly phenomenologically different from the spontaneous and direct experience that emotion in a natural setting (Mayberg *et al.*, 1997). Another potential explanation of the infrequency of amygdala activation in emotional recall may be due to the temporal relationship between changes in blood flow and the behavior in question. Also, the induction of emotions by recall or imagery may be more time-consuming than more direct perceptual induction, making differences in amygdalar responses difficult to detect in PET studies due to limited temporal resolution, or the time-consuming process may be susceptible to known habituation effects (Breiter *et al.*, 1996).

CAVEATS AND LIMITATIONS OF REVIEW

Meta-analysis methodologies in general, and this review in particular, have a number of limitations worth discussing. First, in the search for potential associations between emotion and brain activation, authors may be biased in reporting certain activations. For example, because the associations between fear and the amygdala and between sadness and the subcallosal anterior cingulate cortex have gained attention in activation studies of emotion, studies may under-report failures to find the expected activations, and consequently inflate the probability of finding such associations in a meta-analysis. Second, there is substantial difficulty in examining results from non-uniform experiments. Emotion activation studies differ widely not only in the evocative stimulus, induction method, and emotional tasks employed but also in their statistical power, in the criteria used in defining significant results, and in methods of preprocessing imaging data. Such factors may affect the results considerably and add to the diverse activation patterns throughout the entire brain. Third, there are limitations of the subtraction method, which produced all the activation foci examined in this review. The subtraction method is limited because it does not identify all the regions that are involved in certain emotion/emotional task but only those that show a significant difference between the target and reference condition. Consequently, the re-

sults are confounded if the process of interest is not successfully isolated (Jennings *et al.*, 1997).

Based on the distribution of all activation peaks represented in the brain renderings (Fig. 1), one alternative interpretation is that emotional tasks involve multiple regions throughout the entire brain and do not conclusively point to any particular functional specialization, and that these regions are not disproportionately important to any one emotion. This interpretation would suggest that brain regions are not committed to specific emotions or induction method, but rather may be involved in a variety of emotional, cognitive-emotion, or nonemotional executive tasks. However, comparisons using frequency of activation (percentage of studies reporting) and chi-square analyses (Fig. 2) provide support the associations we have identified in this review. It should be reasonable to expect that significant results from separate independent studies would be reliable data. Nevertheless, we consider the associations identified in this meta-analysis as preliminary and would caution readers against premature conclusions about functional specialization.

We also acknowledge other limitations specific to this review. First, while we separated "Emotion Alone" tasks from those with "Cognitive Demand" in order to examine the effect of a cognitive "nonemotional" component on passive emotional responses, this classification can be argued as somewhat arbitrary. Some tasks labeled as "with Cognitive Demand" (e.g., gender identification) may be regarded as a noncognitively demanding. We would argue that when compared to passive emotional tasks (e.g., viewing emotional faces alone), such acts require that subjects make an overt discrimination/categorization and add a decision-making component, thereby rendering it more "cognitive" than passive viewing (even if the additional cognitive load may be small). However, the heterogeneity of cognitive tasks employed by different experiments should be kept in mind when interpreting the results. Second, we did not include imaging studies examining fear, aversive, and trace conditioning in this review, mainly because the acquisition and extinction tasks examined in these paradigms are not comparable to the other emotional tasks employed by the 55 studies included in our database. If included, there may have been additional evidence for the association between fear and the amygdala, which is supported by the findings of Büchel and Dolan (2000) in their review of this literature. We acknowledge that the decision not to include findings from conditioning studies may have affected the results of this review. Finally, the limited representation of certain induction methods (e.g., auditory) and individual emotions (e.g., anger, disgust) lowers the statistical power to further detect functional anatomic specificity.

CONCLUSION

To our knowledge, this is the first meta-analysis of functional neuroimaging studies involving emotion. Using data obtained from a collection of studies, we examined if specific brain regions were associated with emotional activation in general, different emotions, different induction methods, and cognitive emotional tasks. Our meta-analysis yielded the following summary observations: (1) The medial prefrontal cortex appeared to have a general role in emotional processing across all categories and domains of interest; (2) fear specifically engaged the amygdala; (3) sadness was associated with activity in the subcallosal cingulate; (4) induction by visual stimuli activated the occipital cortex and the amygdala; (5) induction by emotional recall/imagery recruited the anterior cingulate and insula; (6) emotional tasks with cognitive demand particularly involved the anterior cingulate and insula. Our meta-analysis further delineates discrete brain regions that are involved in various emotional tasks. 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.

Several methodological approaches would potentially improve the reliability and validity of identifying specific brain regional involvement in emotion and the ability to make meaningful comparisons across studies in subsequent meta-analyses. Future studies could use more uniform, standard stimuli and design activation paradigms with careful exact isolation of the emotional process of interest. The effect of individual differences in brain activation could be examined by parametric or factorial designs (e.g., correlation with behavioral/physiologic indices) or by personality and temperament measures. Specific activations could be further isolated through "conjunction" and "network" analyses or event-related designs (Cabeza and Nyberg, 2000). 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 review are important constituents of the functional neuroanatomy of emotion.

REFERENCES

- Abercrombie, H. C., Schaefer, S. M., Larson, C. L., Ward, R. T., Holden, J. F., Turski, P. A., Perlman, S. B., and Davidson, R. J. 1996. Medial prefrontal and amygdalar glucose metabolism in depressed and control subjects: an FDG-PET study. *Psychophysiology* **33**: S17.
- Adolphs, R., Tranel, D., Damasio, H., and Damasio, A. R. 1995. Fear and the human amygdala. *J. Neurosci.* **15**: 5879–5891.
- Adolphs, R., Damasio, H., Tranel, D., and Damasio, A. R. 1996. Cortical systems for the recognition of emotion in facial expressions. *J. Neurosci.* **16**: 7678–7687.

- Aggleton, J. P., and Mishkin, M. 1990. Visual impairments in macaques following inferior temporal lesions are exacerbated selectively by additional damage to superior temporal sulcus. *Behav. Brain Res.* **39**: 262–274.
- Amaral, D. G., and Price, J. L. 1984. Amygdalo-cortical projections in the monkey (*Macaca fascicularis*). *J. Comp. Neurol.* **230**: 465–496.
- Anderson, S. W., Bechara, A., Damasio, H., Tranel, D., and Damasio, A. R. 1999. Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nat. Neurosci.* **2**: 1032–1037.
- Augustine, J. R. 1996. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res. Brain Res. Rev.* **229**: 229–244.
- Baker, S. C., Frith, C. D., and Dolan, R. J. 1997. The interaction between mood and cognitive function studied with PET. *Psychol. Med.* **27**: 565–78.
- Baxter, L. R. Jr., Phelps, M. E., Mazziotta, J. C., Schwartz, J. M., Gerner, R. H., Selin, C. E., and Sumida, R. M. 1985. Cerebral metabolic rates for glucose in mood disorders. Studies with positron emission tomography and fluorodeoxyglucose F 18. *Arch. Gen. Psychiatry.* **42**: 441–447.
- Beauregard, M., Chertkow, H., Bub, D., Murtha, S., Dixon, R., and Evans, A. 1997. The neural substrate for concrete, abstract, and emotional word lexica: A positron emission tomography study. *J. Cognit. Neurosci.* **9**: 441–461.
- Beauregard, M., Leroux, J. M., Bergman, S., Yervant, A., Gilles, G., Bourgoin, P., and Stip, E. 1998. The functional neuroanatomy of major depression: An fMRI study using an emotional activation paradigm. *NeuroReport* **9**: 3253–3258.
- Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., and Damasio, A. R. 1995. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science* **269**: 1115–1118.
- Blair, R. J. R., Morris, J. S., Frith, C. D., Perrett, D. I., and Dolan, R. J. 1999. Dissociable neural responses to facial expressions of sadness and anger. *Brain* **122**: 883–893.
- Blood, A. J., Zatorre, R. J., Bermudez, P., and Evans, A. C. 1999. Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. *Nat. Neurosci.* **2**: 382–387.
- Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kenedy, W. A., Rauch, S. L., Buckner, R. L., Strauss, M. M., Hyman, S. E., and Rosen, B. R. 1996. Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* **17**: 875–887.
- Breiter, H. C., Gollub, R. L., Weisskoff, R. M., Kennedy, D. N., Makris, N., Berke, J. D., Goodman, J. M., Kantor, H. L., Gastfriend, D. R., Riorden, J. P., Mathew, R. T., Rosen, B. R., and Hyman, S. E. 1997. Acute effects of cocaine on human brain activity and emotion. *Neuron* **19**: 591–611.
- Bremner, J. D., Staib, L. H., Kaloupek, D., Southwick, S. M., Soufer, R., and Charney, D. S. 1999. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: A positron emission tomography study. *Biol. Psychiatry* **45**: 806–816.
- Brody, A. L., Saxena, S., Silverman, D. H., Alborzian, S., Fairbanks, L. A., Phelps, M. E., Huang, S. C., Wu, H. M., Maidment, K., and Baxter, L. R. Jr. 1999. Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psychiatry Res.* **91**: 127–139.
- Büchel, C., Morris, J., Dolan, R. J., and Friston, K. J. 1998. Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron* **20**: 947–957.
- Büchel, C., Dolan, R. J., Armony, J. L., and Friston, K. J. 1999. Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. *J. Neurosci.* **19**: 10869–10876.
- Büchel, C., and Dolan, R. J. 2000. Classical fear conditioning in functional neuroimaging. *Curr. Opin. Neurobiol.* **10**: 219–223.
- Bush, G., Luu, P., and Posner, M. I. 2000. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn. Sci.* **4**: 215–222.
- Cabeza, R., and Nyberg, L. 2000. Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J. Cogn. Neurosci.* **12**: 1–47.
- Calder, A. J., Young, A. W., Rowland, D., Perrett, D. I., Hodges, J. R., and Etcoff, N. L. 1996. Facial emotion recognition after bilateral amygdala damage: Differentially severe impairment of fear. *Cogn. Neuropsychol.* **13**: 699–745.
- Canli, T., Desmond, J. E., Zhao, Z., Glover, G., and Gabrieli, J. D. 1998. Hemispheric asymmetry for emotional stimuli detected with fMRI. *NeuroReport* **9**: 3233–3239.
- Casey, K. L., Minoshima, S., Berger, K. L., Koeppe, R. A., Morrow, T. J., and Frey, K. A. 1994. Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli. *J. Neurophysiol.* **71**: 802–807.
- Cechetto, D. F., and Saper, C. B. 1990. Role of the cerebral cortex in autonomic function. In *Central Regulation of Autonomic Functions* (A. D. Loewy and K. M. Spyer, Eds.) Oxford Univ. Press, New York.
- Corbetta, M., Miezin, F. M., Shulman, G. L., and Petersen, S. E. 1993. A PET study of visuospatial attention. *J. Neurosci.* **13**: 1202–1226.
- Crosson, B., Randonovich, K., Sadek, J. R., Gokcay, D., Bauer, R., Fischler, I., Cato, M. A., Maron, L., Auerbach, E. J., Browd, S. R., and Briggs, R. W. 1999. Left-hemisphere processing of emotional connotation during word generation. *NeuroReport* **10**: 2449–2455.
- Damasio, A. R. 1994. *Descartes' Error: Emotion, Reason, and the Human Brain*. Avon Books, New York.
- Damasio, A. R., Grabowski, T. J., Bechara, A., Damasio, H., Ponto, L. L. B., Parvizi, J., and Hichwa, R. D. 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nat. Neurosci.* **3**: 1049–1056.
- Davidson, R. J., Ekman, P., Saron, C., Senulis, J., and Friesen, W. V. 1990. Approach/withdrawal and cerebral asymmetry: Emotional expression and brain physiology. *I. J. Pers. Soc. Psychol.* **58**: 330–341.
- Davidson, R. J., and Irwin, W. 1999. The functional neuroanatomy of emotion and affective style. *Trends Cogn. Sci.* **3**: 11–21.
- Davis, M., and Whalen, P. J. 2001. The amygdala: Vigilance and emotion. *Mol. Psychiatry* **6**: 13–34.
- Devinsky, O., Morrell, M. J., and Vogt, B. A. 1995. Contributions of anterior cingulate cortex to behaviour. *Brain* **118**: 279–306.
- Dolan, R. J. 1998. A cognitive affective role for the cerebellum. *Brain* **121**: 545–546.
- Dolan, R. J., Lane, R., Chua, P., and Fletcher, P. 2000. Dissociable temporal lobe activations during emotional episodic memory retrieval. *NeuroImage* **11**: 203–209. doi:10.1006/nimg.2000.0538.
- Dougherty, D. D., Shin, L. M., Alpert, N. M., Pitman, R. K., Orr, S. P., Lasko, M., Macklin, M. L., Fischman, A. J., and Rauch, S. L. 1999. Anger in healthy men: A PET study using script-driven imagery. *Biol. Psychiatry* **46**: 466–472.
- Drevets, W. C., Price, J. L., Simpson, J. R., Jr, Todd, R. D., Reich, T., Vannier, M., and Raichle, M. E. 1997. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* **386**: 824–827.
- Drevets, W. C., and Raichle, M. E. 1998. Reciprocal Suppression of Regional Cerebral Blood Flow during Emotional versus Higher Cognitive Processes: Implications for interaction between Emotion and Cognition. *Cogn. Emotion* **12**: 353–385.

- Duncan, J., and Owen, A. M. 2000. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci.* **23**: 475–483.
- Everitt, B. J., Morris, K. A., O'Brien, A., and Robbins, T. W. 1991. The basolateral amygdala-ventral striatal system and conditioned place preference: Further evidence of limbic-striatal interactions underlying reward-related processes. *Neuroscience* **42**: 1–18.
- Fox, P. T., Parson, L. M., and Lancaster, J. L. 1998. Beyond the single study: Function/location metanalysis in cognitive neuroimaging. *Curr. Opin. Neurobiol.* **8**: 178–187.
- Frey, S., Kostopoulos, P., and Petrides, M. 2000. Orbitofrontal involvement in the processing of unpleasant auditory information. *Eur. J. Neurosci.* **12**: 3709–3712.
- Gemar, M. C., Kapur, S., Segal, Z. V., Brown, G. M., and Houle, S. 1996. Effects of self-generated sad mood on regional cerebral activity: A PET study in normal subjects. *Depression* **4**: 81–88.
- George, M. S., Ketter, T. A., Gil, D. S., Haxby, J. V., Ungerleider, L. G., and Herscovitch, P., and Post, R. 1993. Brain regions involved in recognizing facial emotion or identity: An oxygen-15 PET study. *J. Neuropsychiatry Clin. Neurosci.* **5**: 384–394.
- George, M. S., Ketter, T. A., Parekh, P. I., Horwitz, B., Herscovitch, P., and Post, R. M. 1995. Brain activity during transient sadness and happiness in healthy women. *Am. J. Psychiatry* **152**: 341–351.
- George, M. S., Parekh, P. I., Rosinsky, N., Ketter, T. A., Kimbrell, T. A., Heilman, K. M., Herscovitch, P., and Post, R. M. 1996a. Understanding emotional prosody activates right hemisphere regions. *Arch. Neurol.* **53**: 665–670.
- George, M. S., Ketter, T. A., Parekh, P. I., Herscovitch, P., and Post, R. M. 1996b. Gender differences in regional cerebral blood flow during transient self-induced sadness or happiness. *Biol. Psychiatry* **40**: 859–871.
- Gray, J. A. 1982. *The Neuropsychology of Anxiety*. Oxford Univ. Press, New York.
- Halgren, E., Walter, R. D., Cherlow, D. G., and Crandall, P. H. 1978. Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdala. *Brain* **101**: 83–117.
- Hamann, S. B., Ely, T. D., Grafton, S. T., and Kilts, C. D. 1999. Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nat. Neurosci.* **2**: 289–293.
- Hariri, A. R., Bookheimer, S. Y., and Mazziotta, J. C. 2000. Modulating emotional responses: Effects of a neocortical network on the limbic system. *NeuroReport* **11**: 43–48.
- Hutchinson, M., Schiffer, W., Joseffer, S., Liu, A., Schlosser, R., Dikshit, S., Goldberg, E., and Brodie, J. D. Task-specific deactivation patterns in functional magnetic resonance imaging. *Magn. Reson. Imag.* **17**: 1427–1436.
- Irwin, W., Davidson, R. J., Lowe, M. J., Mock, B. J., Sorenson, J. A., and Turski, P. A. 1996. Human amygdala activation detected with echo-planar functional magnetic resonance imaging. *NeuroReport* **7**: 1765–1769.
- Isenberg, N., Silbersweig, D., Engelien, A., Emmerich, S., Malavade, K., Beattie, B., Leon, A. C., and Stern, E. 1999. Linguistic threat activates the human amygdala. *Proc. Natl. Acad. Sci. USA* **96**: 10456–10459.
- Iwai, E., Yukie, M., Suyama, H., and Shirakawa, S. 1987. Amygdalar connections with middle and inferior temporal gyri of the monkey. *Neurosci. Lett.* **83**: 25–9.
- Jennings, J. M., McIntosh, A. R., Kapur, S., Tulving, E., and Houle, S. 1997. Cognitive subtractions may not add up: The interaction between semantic processing and response mode. *NeuroImage* **5**: 229–239.
- Kalin, N. H., Davidson, R. J., Irwin, W., Warner, G., Orendi, J. L., Sutton, S. K., Mock, B. J., Sorenson, J. A., Lowe, M., and Turski, P. A. 1997. Functional magnetic resonance imaging studies of emotional processing in normal and depressed patients: Effects of venlafaxine. *J. Clin. Psychiatry* **58**(S16): 32–39.
- Ketter, T. A., Andreason, P. J., George, M. S., Lee, C., Gill, D. S., Parekh, P. I., Willis, M. W., Herscovitch, P., and Post, R. M. 1996. Anterior paralimbic mediation of procaine-induced emotional and psychosensory experiences. *Arch. Gen. Psychiatry* **53**: 59–69.
- Kimbrell, T. A., George, M. S., Parekh, P. I., Ketter, T. A., Podell, D. M., Danielson, A. L., Repella, J. D., Benson, B. E., Willis, M. W., Herscovitch, P., and Post, R. M. 1999. Regional brain activity during transient self-induced anxiety and anger in healthy adults. *Biol. Psychiatry* **46**: 454–65.
- King, A. S., and Brothers, L. A. 1992. *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction* (J. P. Aggleton, Ed.), pp. 355–377. Wiley-Liss, New York.
- Kluver, H., and Bucy, P. C. 1939. Preliminary analysis of functions of the temporal lobes in monkeys. *Arch. Neurol. Psychiatry* **42**: 979–1000.
- Koch, M., Schmid, A., and Schnitzer, H. U. 1996. Pleasure-attenuation of startle is disrupted by lesions of the nucleus accumbens. *NeuroReport* **7**: 1442–1446.
- Koepp, M. J., Gunn, R. N., Lawrence, A. D., Cunningham, V. J., Dagher, A., Jones, T., Brooks, D. J., Bench, C. J., and Grasby, P. M. 1998. Evidence for striatal dopamine release during a video game. *Nature* **393**: 266–268.
- Koob, G. F. 1992. Neurobiological mechanisms of cocaine and opiate dependence. In *Addictive States* (C. P. O'Brien and J. H. Faffe, Eds.) Raven Press, New York.
- Kosslyn, S. M., Shin, L. M., Thompson, W. L., McNally, R. J., Rauch, S. L., Pitman, R. K., and Alpert, N. M. 1996. Neural effects of visualizing and perceiving aversive stimuli: A PET investigation. *NeuroReport* **7**: 1569–1576.
- LaBar, K. S., LeDoux, J. E., Spencer, D. D., and Phelps, E. A. 1995. Impaired fear condition following unilateral temporal lobectomy in humans. *J. Neurosci.* **15**: 6846–6855.
- LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E., and Phelps, E. A. 1998. Human amygdala activation during conditioned fear acquisition and extinction: A mixed-trial fMRI study. *Neuron* **20**: 937–945.
- Lane, R. D., Reiman, E. M., Ahern, G. L., Schwartz, G. E., and Davidson, R. J. 1997a. Neuroanatomical correlates of happiness, sadness, and disgust. *Am. J. Psychiatry* **154**: 926–933.
- Lane, R. D., Reiman, E. M., Bradley, M. M., Lang, P. J., Ahern, G. L., Davidson, R. J., and Schwartz, G. E. 1997b. Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia* **35**: 1437–1444.
- Lane, R. D., Fink, G. R., Chau, P. M., and Dolan, R. J. 1997c. Neural activation during selective attention to subjective emotional responses. *NeuroReport* **8**: 3969–3972.
- Lane, R. D., Reiman, E. M., Axelrod, B., Yun, L. S., Holmes, A., and Schwartz, G. E. 1998. Neural correlates of levels of emotional awareness. Evidence of an interaction between emotion and attention in the anterior cingulate cortex. *J. Cogn. Neurosci.* **10**: 525–35.
- Lane, R. D., Chua, P. M., and Dolan, R. J. 1999. Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures. *Neuropsychologia* **37**: 989–997.
- Lane, R. D., and Nadel, L. (Eds.) 2000. *Cognitive Neuroscience of Emotion*. Oxford Univ. Press, New York.
- Lang, P. J., Greenwald, M. K., Bradley, M. M., and Hamm A. O. 1993. Looking at pictures: Affective, facial, visceral, and behavioral reactions. *Psychophysiology* **30**: 261–273.
- Lang, P. J., Bradley, M. M., Fitzsimmons, J. R., Cuthbert, B. N., Scott, J. D., Moulder, B., and Nangia, V. 1998. Emotional arousal and activation of the visual cortex: An fMRI analysis. *Psychophysiology* **35**: 199–210.

- LeDoux, J. E. 1993. Emotional memory systems in the brain. *Behav. Brain Res.* **58**: 69–79.
- LeDoux, J. E. 1996. *The Emotional Brain*. Simon & Schuster, New York.
- LeDoux, J. E. 2000. Emotion circuits in the brain. *Annu. Rev. Neurosci.* **23**: 155–184.
- Liberzon, I., Taylor, S. F., Fig, L. M., Decker, L. R., Koeppe, R. A., and Minoshima, S. 2000. Limbic activation and psychophysiologic responses to aversive visual stimuli. Interaction with cognitive task. *Neuropsychopharmacology* **23**: 508–516.
- Liotti, M., Mayberg, H. S., Brannan, S. K., McGinnis, S., Jerabek, P., and Fox, P. T. 2000. Differential limbic–cortical correlates of sadness and anxiety in healthy subjects: Implications for affective disorders. *Biol. Psychiatry* **48**: 30–42.
- MacLean, P. D. 1952. Some psychiatric implications of physiological studies on the frontotemporal portion of limbic system (visceral brain). *Electroencephalogr. Clin. Neurophysiol.* **4**: 407–418.
- Maddock, R. J., and Buonocore, M. H. 1997. Activation of left posterior cingulate gyrus by the auditory presentation of threat-related words: An fMRI study. *Psychiatry Res.* **75**: 1–14.
- Maddock, R. J. 1999. The retrosplenial cortex and emotion: New insights from functional neuroimaging of the human brain. *Trends Neurosci.* **22**: 310–316.
- Mayberg, H. S., Lewis, P. J., Regenold, W., and Wagner, H. N. Jr. 1994. Paralimbic hypoperfusion in unipolar depression. *J. Nucl. Med.* **35**: 929–934.
- Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. A., Silva, J. A., Tekell, J. L., Martin, C. C., Lancaster, J. L., and Fox, P. T. 1999. Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. *Am. J. Psychiatry* **156**: 675–82.
- Mayberg, H. S., Brannan, S. K., Tekell, J. L., Silva, J. A., Mahurin, R. K., McGinnis, S., and Jerabek, P. A. 2000. Regional metabolic effects of fluoxetine in major depression: Serial changes and relationship to clinical response. *Biol. Psychiatry*. 2000 **48**: 830–843.
- Morgan, M. A., Romanski, L. M., and LeDoux, J. E. 1993. Extinction of emotional learning: Contribution of medial prefrontal cortex. *Neurosci. Lett.* **163**: 109–113.
- Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J., and Dolan, R. J. 1996. A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature* **383**: 812–815.
- Morris, J. S., Friston, K. J., Büchel, C., Frith, C. D., Young, A. W., Calder, A. J., and Dolan, R. J. 1998a. A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain* **121**: 47–57.
- Morris, J. S., Ohman, A., and Dolan, R. J. 1998b. Conscious and unconscious emotional learning in the human amygdala. *Nature* **393**: 467–470.
- Morris, J. S., Scott, S. K., and Dolan, R. J. 1999. Saying it with feeling: Neural responses to emotional vocalizations. *Neuropsychologia* **37**: 1155–1163.
- Nakamura, K., Kawashima, R., Ito, K., Sugiura, M., Kato, T., Nakamura, A., Hatano, K., Nagumo, S., Kutoba, K., Fukuda, H., and Kojima, S. 1999. Activation of the right inferior frontal cortex during assesment of facial emotion. *J. Neurophysiol.* **82**: 1610–1614.
- O'Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J., and Andrews, C. 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat. Neurosci.* **4**: 95–102.
- Panksepp, J. 1998. *Affective Neuroscience: The Foundations of Human and Animal Emotions*. Oxford Univ. Press, New York.
- Papez, J. W. 1937. A proposed mechanism of emotion. *Arch. Neurol. Psychiatry* **38**: 725–743.
- Paradiso, S., Robinson, R. G., Andreasen, N. C., Downhill, J. E., Davidson, R. J., Kirchner, P. T., Watkins, G. L., Ponto, L. L., and Hichwa, R. D. 1997. Emotional activation of limbic circuitry in elderly normal subjects in a PET study. *Am. J. Psychiatry*. **154**: 384–389.
- Paradiso, S., Johnson, D. L., Andreasen, N. C., O'Leary, D. S., Watkins, G. L., Ponto, L. L., and Hichwa, R. D. 1999. Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. *Am. J. Psychiatry* **156**: 1618–1629.
- Pardo, J. V., Pardo, P. J., and Raichle, M. E. 1993. Neural correlates of self-induced dysphoria. *Am. J. Psychiatry* **150**: 713–719.
- Partiot, A., Grafman, J., Sadato, N., Wachs, J., and Hallett, M. 1995. Brain activation during the generation of non-emotional and emotional plans. *NeuroReport* **6**: 1397–1400.
- Petrides, M., and Pandya, D. N. 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *Eur. J. Neurosci.* **11**: 1011–1036.
- Pietrini, P., Guazzelli, M., Basso, G., Jaffe, K., and Grafman, J. 2000. Neural correlates of imaginal aggressive behavior assessed by positron emission tomography in healthy subjects. *Am. J. Psychiatry* **157**: 1772–1781.
- Phillips, M. L., Young, A. W., Senior, C., Brammer, M., Andrew, C., Calder, A. J., Bullmore, E. T., Perrett, D. I., Rowland, D., Williams, S. C., Gray, J. A., and David, A. S. 1997. A specific neural substrate for perceiving facial expressions of disgust. *Nature* **389**: 495–498.
- Phillips, M. L., Young, A. W., Scott, S. K., Calder, A. J., Andrew, C., Giampietro, V., Williams, S. C., Bullmore, E. T., Brammer, M., and Gray, J. A. 1998a. Neural responses to facial and vocal expressions of fear and disgust. *Proc. R. Soc. Lond. B. Biol. Sci.* **265**: 1809–17.
- Phillips, M. L., Bullmore, E. T., Howard, R., Woodruff, P. W. R., Wright, I. C., Williams, S. C. R., Simmons, A., Andrew, C., Brammer, M., and David, A. S. 1998b. Investigation of facial recognition memory and happy and sad facial expression perception: an fMRI study. *Psychiatry Res. Neuroimag.* **83**: 127–138.
- Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., and Shulman, G. L. 2001. Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Pro. Natl. Acad. Sci. USA* **98**: 676–682.
- Rauch, S. L., Shin, L. M., Dougherty, D. D., Alpert, N. M., Orr, S. P., Lasko, M., Macklin, M. L., Fischman, A. J., and Pitman, R. K. 1999. Neural activation during sexual and competitive arousal in healthy men. *Psychiatry Res. Neuroimag. Section* **91**: 1–10.
- Redoute, J., Stoleru, S., Gregoire, M., Costes, N., Cinotti, L., Lavenne, F., Le Bars, D., Forest, M., and Pujol, J. 2000. Brain processing of visual sexual stimuli in human males. *Hum. Brain Mapp.* **11**: 162–177.
- Reiman, E. M., Fusselman, M. J., Fox, P. T., and Raichle, M. E. 1989a. Neuroanatomical correlates of anticipatory anxiety. *Science* **243**: 1071–1074.
- Reiman, E. M., Raichle, M. E., and Robins, E. 1989b. Involvement of the temporal poles in pathological and normal forms of anxiety. *J. Cereb Blood Flow Metab.* **9**: S589.
- Reiman, E. M., Lane, R. D., Ahern, G. L., Schwartz, G. E., Davidson, R. J., Friston, K. J., Yun, L. S., and Chen, K. 1997. Neuroanatomical correlates of externally and internally generated human emotion. *Am. J. Psychiatry* **154**: 918–925.
- Rolls, E. T. 1999. *The Brain and Emotion*. Oxford Univ. Press, New York.
- Rolls, E. T. 2000. The orbitofrontal cortex and reward. *Cereb. Cortex* **10**: 284–294.
- Royet, J. P., Zald, D., Versace, R., Costes, N., Lavenne, F., Koenig, O., and Gervais, R. 2000. Emotional responses to pleasant and un-

- pleasant olfactory, visual, and auditory stimuli: A positron emission tomography study. *J. Neurosci.* **20**: 7752–7759.
- Rozin, P., and Fallon, A. E. 1987. A perspective on disgust. *Psychol. Rev.* **94**: 23–41.
- Scott, S. K., Young, A. W., Calder, A. J., Hellawell, D. J., Aggleton, J. P., and Johnson, M. 1997. Impaired auditory recognition of fear and anger following bilateral amygdalar lesions. *Nature* **385**: 254–257.
- Shin, L. M., Dougherty, D. D., Orr, S. P., Pitman, R. K., Lasko, M., Macklin, M. L., Alpert, N. M., Fischman, A. J., and Rauch, S. L. 2000. Activation of anterior paralimbic structures during guilt-related script-driven imagery. *Biol. Psychiatry* **48**: 43–50.
- Simpson, J. R., Ongur, D., Akbudak, E., Conturo, T. E., Ollinger, J. M., Snyder, A. Z., Gusnard, D. A., and Raichle, M. E. 2000. The emotional modulation of cognitive processing: An fMRI study. *J. Cogn. Neurosci.* **12**(S2): 157–170.
- Small, D. M., Zald, D. H., Jones-Gotman, M., Zatorre, R. J., Parado, J. V., Frey, S., and Petrides, M. 1999. Human cortical gustatory areas: A review of functional neuroimaging data. *NeuroReport* **10**: 7–14.
- Sprengelmeyer, R., Young, A. W., Calder, A. J., Karnat, A., Lange, H. W., Homberg, V., Perret, D. I., and Rowland, D. 1996. Loss of disgust: Perception of faces and emotions in Huntington's disease. *Brain* **119**: 1647–1665.
- Sprengelmeyer, R., Young, A. W., Sprengelmeyer, A., Calder, A. J., Rowland, D., Perret, D. I., Homberg, V., and Lange, H. W. 1997. Recognition of facial expressions: Selective impairment of specific emotions in Huntington's disease. *Cogn. Neuropsychol.* **14**: 839–879.
- Sprengelmeyer, R., Rausch, M., Eysel, U. T., and Przuntek, H. 1998. Neural structures associated with recognition of facial expressions of basic emotions. *Proc. R. Soc. Lond. B. Biol. Sci.* **265**: 1927–31.
- Stein, E. A., Pankiewicz, J., Harsch, H. H., Cho, J. K., Fuller, S. A., Hoffmann, R. G., Hawkins, M., Rao, S. M., Bandettini, P. A., and Bloom, A. S. 1998. Nicotine-induced limbic cortical activation in the human brain: A functional MRI study. *Am. J. Psychiatry* **155**: 1009–1015.
- Talairach, J., and Tournoux, P. 1988. *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme Medical, New York.
- Taylor, S. F., Liberzon, I., Fig, L. M., Decker, L. R., Minoshima, S., and Koeppe, R. A. 1998. The effect of emotional content on visual recognition memory: A PET activation study. *NeuroImage* **8**: 188–197.
- Taylor, S. F., Liberzon, I., and Koeppe, R. A. 2000. The effect of graded aversive stimuli on limbic and visual activation. *Neuropsychologia* **38**: 1415–1425.
- Teasdale, J. D., Howard, R. J., Cox, S. G., Ha, Y., Brammer, M. J., Williams, S. C. R., and Checkley, S. A. 1999. Functional MRI study of the cognitive generation of affect. *Am. J. Psychiatry* **156**: 209–215.
- Weiskrantz, L. 1956. Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *J. Comp. Physiol. Psychol.* **49**: 381–391.
- Whalen, P. J., Bush, G., McNally, R. J., Wilhelm, S., McInerney, S. C., Jenike, M. A., and Rauch, S. L. 1998a. The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol. Psychiatry* **44**: 1219–1228.
- Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., and Jenike, M. A. 1998b. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J. Neurosci.* **18**: 411–418.