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Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging

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Abstract

We performed quantitative meta-analyses on 65 neuroimaging studies of emotion. In an earlier report (NeuroImage 16 (2002), 331). we examined the effects of induction method, specific emotions, and cognitive demand in emotional tasks. This paper focuses on the effects of emotional valence (positive vs negative and approach vs withdrawal) and gender on regional brain activations, with particular emphasis on hypotheses concerning lateralization of brain function in emotion. Overall, we found no support for the hypothesis of overall right-lateralization of emotional function, and limited support for valence-specific lateralization of emotional activity in frontal cortex. In addition, we found that males showed more lateralization of emotional activity, and females showed more brainstem activation in affective paradigms. The study provides evidence that lateralization of emotional activity is more complex and region-specific than predicted by previous theories of emotion and the brain.

Introduction

In recent years, the number of studies devoted to the study of emotion using functional neuroimaging has increased dramatically; however, single studies usually provide limited insight into the function of specific brain regions (Sarter et al., 1996). Making inferences about regional brain function requires not only knowledge that a brain structure may be active during a certain task, but also knowledge of the range of tasks that activates an area and the kinds of tasks that do *not* activate it. While several reviews have permitted some synthesis of imaging results in the cognitive domain, no such relatively comprehensive review exists for neuroimaging studies of emotion. In the initial part of our review, we provided a meta-analysis of activations related to individual emotions, induction methods, and cognitive demand (Phan et al., 2002). In this paper, we focus specifically on examining neuroimaging evidence pertaining to several existing hypotheses about the lateralization of emotion and gender effects in the brain, using meta-analytic approaches based on the distribution of reported activation peaks in space. These hypotheses were formed before the advent of functional brain imaging, and as a result have been developed at a very broad level of anatomical resolution, typically at the level of the cerebral hemisphere. Functional imaging allows those hypotheses to be tested at both general and more specific levels of spatial detail. We introduce the hypotheses below.

Theories of emotion in the brain

Overall right-hemisphere dominance in emotion

One of the oldest theories of emotion in the brain is that the left hemisphere is specialized for a number of cognitive processes, and the right hemisphere is predominantly involved in processing emotion. Behavioral studies have shown that in healthy humans, the left side of the face is emotionally more expressive (Sackeim et al., 1978); emotional intonation (prosody) is more easily recognized when presented to the left ear (Erhan et al., 1998), and stimuli presented in the left visual field (i.e., first to the right hemisphere) are judged as more emotional (Levine and Levy, 1986) and elicit greater autonomic responses (Spence et al., 1996). Deficits in prosody (emotional speech charac-

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teristics) have been found in patients with right hemisphere frontal damage (Ross and Mesulam, 1979), and deficits in recognition of emotional facial expressions have been linked to right hemisphere damage (Mandal et al., 1996; Weddell, 1994). However, a number of studies have failed to find lateralization of emotion (Caltagirone et al., 1989; Kowner, 1995; Mammucari et al., 1988; Mandal et al., 1992), and there is substantial variability among different lateralization indices (Boles, 1996). Most of these studies have used relatively crude proxy measures for lateralization; however, they provide the basis for the first hypothesis in our review, that emotions are lateralized by hemisphere. We also tested a more plausible variation on this hypothesis, that emotional activations and emotional lateralization are confined to specific brain regions.

Valence lateralization hypothesis

A more recent conceptualization is that both hemispheres process emotion, but each hemisphere is specialized for particular types of emotion, particularly in the lateral frontal cortex. In one formulation, the left hemisphere is dominant for positive emotions and the right hemisphere is dominant for negative emotions (Davidson, 1992; Gur et al., 1994; Robinson and Starkstein, 1989; Sackeim et al., 1978, 1982). A disproportionate number of patients who have suffered trauma to the left frontal lobe, particularly to the lateral prefrontal cortex or basal ganglia, become depressed (e.g., Morris et al., 1996; Paradiso et al., 1999; Sackeim et al., 1982). Patients with right frontal damage, however, are more likely to show signs of inappropriate cheerfulness and mania (Starkstein et al., 1989). Behavioral studies have reinforced this notion, showing that processing of positive emotions is potentiated when emotional stimuli are presented to the left hemisphere, and negative emotions are potentiated when presented to the right hemisphere (Burton and Levy, 1989; Davidson et al., 1987).

A more recent set of EEG experiments has provided some support for the idea that positive and negative emotions are lateralized, especially in the frontal cortex (Davidson and Fox, 1982; Tucker et al., 1981), and very early in development (Davidson and Fox, 1982; Fox and Davidson, 1986). Davidson and colleagues have proposed that lateralization, particularly in the anterior frontal cortex, may depend on either transiently induced mood or stable personality traits, termed "affective style" (Davidson, 1993, 1995, 1998; Davidson and Irwin, 1999; Tomarken et al., 1990, 1992). Although both valence and approach/withdrawal dimensions have been used to conceptualize these differences, these studies have tended to favor the more biologically grounded concepts of approach and withdrawal (e.g., Davidson, 1992). The two dimensions overlap substantially, with the greatest difference in the classification of anger. Traditionally considered a negative emotion, anger is often associated with approach behavior.

The evidence supporting the valence lateralization hypothesis has been mixed. Across studies, lesion data have not always supported the hypothesis (Borod, 1992). Several groups have failed to demonstrate valence lateralization in EEG studies (e.g., Collet and Duclaux, 1987; Gotlib et al., 1998; Hagemann et al., 1998; Reid et al., 1998). Our meta-analysis sought to address this controversy. We analyzed lateralization of reported regional brain activations as a function of valence, with particular attention to the lateral frontal cortex. Because recent theory suggests that emotions may be lateralized according to the concepts of approach and avoidance rather than valence, we also used this dichotomy to test the valence lateralization hypothesis.

Gender differences in the functional anatomy of emotion

Several studies have shown that female and male subjects process emotions differently. Women have been found to be more emotionally expressive than men (Kring and Gordon, 1998), possibly as a result of differences in socialization (Grossman and Wood, 1993), and they show stronger psychophysiological responses to emotional stimuli (Kring and Gordon, 1998; Orozco and Ehlers, 1998). Anatomically, women exhibit more gray-matter volume in the cingulate cortex, traditionally a part of the limbic system (Good et al., 2001). Although there are few studies that directly address the underlying functional anatomy of these phenomena, one prediction is that women will show stronger activations in emotional tasks, particularly in areas related to subjective feeling. Accordingly, we tested whether women show more activation for emotional material than men, with a special focus on the anterior cingulate and brainstem.

Gender effects on lateralization of emotion

A second hypothesis about gender effects on emotion concerns the lateralization of emotion in men and women. Some studies have reported that male subjects show more lateralization of brain function than females (Bowers and LaBarba, 1988; Crucian, 1996; Hines et al., 1992; Russo et al., 2000; Steele, 1998; Witelson and Kigar, 1988). Anatomically, men show greater temporal cortex asymmetry (Good et al., 2001). Men and women may also show different patterns of lateralization in emotional processing. Recently, researchers have begun to hypothesize gender effects on emotion-related brain activations, particularly with regard to amygdala activations (Cahill et al., 2001; Killgore et al., 2001; Killgore and Yurgelun-Todd, 2001). Therefore, we tested hypotheses about whether lateralization of emotion varied as a function of gender and region, with particular attention to the amygdala.

Structure of analyses

In order to test these hypotheses, we first categorized the location of each reported activation into one of 11 regions of interest (ROIs), using the anatomical localization as reported by the authors (e.g., middle frontal gyrus, anterior cingulate, etc.), allowing us to test each hypothesis within gross brain structures. In addition, the ROI approach allowed us to explore the question of regional specialization in emotion processing for both gender and valence. In a second analysis, we used the coordinates of reported peaks to compute point-density maps for each condition (e.g., positive and negative valence). Subtracting maps for contrasting conditions (e.g., positive vs negative, male vs female) allowed us to localize regions that showed a condition-specific response without arbitrarily defining ROIs, providing a potentially more sensitive and spatially specific analysis. The analyses were conducted, and are reported, according to the following structure:

Hypothesis 1

Hemispheric lateralization hypothesis: the right hemisphere is more likely to process emotions (main effect of laterality)

Hypothesis 2

Regional activations differ according to emotional valence and/or approach/withdrawal classification

a. Certain regions of the brain exhibit lateralized processing of emotions (laterality × region interaction).

b. Certain regions of the brain are differentially responsive to valence or approach/withdrawal (valence × region interaction).

c. Emotional activations are lateralized differently according to valence in specific brain regions, particularly the lateral frontal cortex (valence × laterality × region interaction).

Hypothesis 3

Females and males show different patterns of brain responses to emotions

a. Females show greater emotional responses overall (main effect of gender).

b. Females show greater emotional responses in some regions, and males show greater responses in some regions (gender × region interaction).

c. Males show greater lateralization in emotional responses, whereas females' responses are more bilateral (gender × laterality interaction).

d. Emotional activations are lateralized differently according to gender in specific brain regions, particularly the amygdala (gender × laterality × region interaction).

Methods

Study selection

We analyzed 65 PET and fMRI studies of emotional tasks published between 1992 and February 2002, listed in Table 1. Studies were identified by searches on two versions of Medline (Medsearch and PubMed) and PsycInfo. Studies were included if they reported whole-brain comparisons of two emotion-eliciting tasks or in comparison to a baseline task, included healthy, unmedicated subjects, and reported standardized coordinates for activation foci in either Montreal Neurologic Institute (MNI) or Talairach (Talairach and Tournoux, 1988) space. We included studies involving constructs typically thought of as emotion, including joy, happiness, sadness, fear, anxiety, anger, guilt, and sexual desire, as well as studies that used pictures or other means to elicit combinations of these. We did not include studies on hunger, thirst, monetary reward, and pain (see reviews by Casey, 1999; Small et al., 1999; see also Breiter et al., 2001). Also not included are studies that focused on cognitive or learning mechanisms as they related to emotional material, such as fear conditioning or reasoning about emotional situations (Buchel and Dolan, 2000). As reported earlier (Phan et al., 2002), we analyzed only positive activations (i.e., no "deactivations").

Data extraction

We extracted activation foci data from the selected studies in two ways. In one, we divided the brain into 11 broad regions of interest, including lateral frontal cortex; medial cortex (including anterior cingulate, supplementary motor cortex, medial prefrontal cortex, and mid- and posterior cingulate); temporal cortex, including hippocampus; posterior cortex, including parietal and occipital lobes; orbitofrontal cortex; insular cortex; basal forebrain (including nucleus accumbens, substantia innominata, septal nuclei, and other sublenticular nuclei); amygdala; brainstem (including the thalamus, midbrain, pons, and medulla); and cerebellum. Peaks were classified into one of these regions based on the area reported by the study authors for each peak. As an alternative, we used the reported coordinates of each focus, translating coordinates reported in true Talairach space (following the 1988 atlas of Talairach and Tournoux) into the similar (but not identical) atlas space of the MNI. For this transformation, we employed a bilinear transformation (developed by Matthew Brett; http://www.mrc-cbu.cam.ac.uk/Imaging/).

Each peak was classified along three dimensions. The *valence* dimension consisted of positive (including happiness, joy, contentment, positive pictures, and sexual stimuli) and negative (including fear, anger, aggression, sadness, guilt, and negative pictures) emotions. The *approach/withdrawal* dimension classified into approach and withdrawal categories the same emotions as for positive and negative, except that anger and aggression were classified as approach emotions. We classified activations derived from only male or only female participants into categories of the *gender* dimension.

Table 1
List of emotion activation studies included in the metaanalysis

Study	Year	Valence			Approach/Withdrawal			Gender		
		Positive	Negative	Mix	Approach	Withdraw	Mix	Female	Male	Both
Baker	1997	X	X		X	X			X	
Beauregard	1997			X			X		X	
Beauregard	2001	X			X				X	
Beauregard	1998		X			X				X
Blair	1999		X	X	X	X	X		X	
Blood	1999		X			X				X
Breiter	1996	X	X	X	X	X	X		X	
Canli	1998	X	X		X	X		X		
Crosson	1999			X			X			X
Damasio	2000	X	X		X	X				X
Dolan	2000			X			X		X	
Dolan	2001		X			X				X
Dougherty	1999		X		X				X	
Frey	2000		X			X		X		
Gemar	1996		X			X			X	
George	1993			X			X	X		
George	1994		X			X				X
George	1995		X			X		X		X
George	1996a			X			X			X
George	1996b	X	X		X	X		X	X	
Gorno-tempini	2001	X	X		X	X				X
Hamann	1999	X	X		X	X			X	
Hariri	2000			X			X			X
Isenberg	1999		X			X				X
Kesler-West	2001		X		X	X				X
Kimbrell	1999		X		X	X				X
Kosslyn	1996		X			X			X	
Lane	1997a	X	X		X	X		X		
Lane	1997b			X			X		X	
Lane	1997c	X	X		X	X		X		
Lane	1998			X			X	X		
Lane	1999	X	X	X	X	X	X		X	
Lang	1998	X	X		X	X				X
Liberzon	2000		X			X		X		
Liotti	2000		X			X		X		
Maddock	1997		X			X				X
Maratos	2001	X	X		X	X				X
Mayberg	1999		X			X		X		
Morris	1996	X	X		X	X				X
Morris	1998	X	X	X	X	X	X			X
Morris	1999		X	X		X	X		X	
Nakamura	1999			X			X		X	
Paradiso	1997	X	X		X	X				X
Paradiso	1999	X	X		X	X				X
Pardo	1993		X			X				X
Partiot	1995		X			X				
Phillips	1997		X			X				X
Phillips	1998a		X			X			X	
Phillips	1998b	X			X					X
Pietrini	2000		X		X					X
Rauch	1999	X			X				X	
Redoute	2000	X			X				X	
Reiman	1997			X			X	X		
Royet	2000			X			X		X	
Shin	2000		X			X			X	
Simpson	2000		X			X				X
Sprengelmeyer	1998		X		X	X				X
Tabert	2001	X	X		X	X		X		
Taylor	2000		X			X				X
Taylor	1998		X			X		X		
Teasdale	1999	X	X		X	X				X
Vuilleumier	2001		X			X				X
Whalen	1998		X			X			X	X
Williams	2001		X			X			X	

Data analysis—regional specificity

Regions of interest

For each region, we calculated two types of summary measures of activation—(number/percentage) of *studies* and (number/percentage) of *peaks.* For *studies,* a count was incremented in a region if the study reported at least one activation peak in that region. For *peaks,* the total number of peaks in the region across all studies was counted. Each method has associated advantages and disadvantages (see Phan et al., 2002, for detailed discussion).

For the whole-brain test of male vs female activations, we counted how many peaks were found in each study conducted on males and females, and then performed a two-sample *t* test on peak counts, treating study as a random variable.

Within each ROI, for both *studies* and *peaks,* we used χ^2 analyses to test whether more than the expected number of observations occurred in this region for each of the three dimensions: *valence*, *approach/withdrawal*, and *gender*. Expectations were based on the total number of points reported in each condition across regions and the total number of activation points across both test conditions.

Density analysis

In our second approach, we used a novel meta-analysis technique that avoids the somewhat arbitrary nature of defining ROIs, as well as the difficulty of properly assigning a peak to the appropriate ROI. Using the stereotactic (MNI) coordinates of each peak, we calculated the density distribution of activation foci throughout the brain, using two dimensions to categorize activations (approach/withdrawal, gender), but excluding valence because of its high redundancy with approach/withdrawal. We calculated the density of reported points by a method similar to the convolution approach proposed by Chein et al. (2001). Density for each voxel in a 2 × 2 × 2 mm standard brain space was calculated as the number of peaks reported within a 10-mm sphere surrounding that coordinate divided by the volume of the sphere. This method is equivalent to the convolution of a 3D mask volume, in which reported points are represented with ones and nonreported points are represented with zeros, with the 10-mm sphere, if the convolution results are appropriately normalized.

After the peak density maps for each condition (e.g., approach and avoidance) were estimated, each one was subtracted from the other to yield two density difference maps, and these density differences were compared with a null-hypothesis distribution created through Monte Carlo simulations. In the simulations, for each condition (e.g., approach and avoidance), the same number of points as were reported for that condition were randomly distributed throughout gray and white matter voxels in the standard MNI brain (avg152T1.img; SPM, Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/) and a density map was calculated from the points. For each random distribution of points, two difference maps were obtained (A − B and B − A), corresponding to greater density (of randomly distributed points) for each condition compared to the other. This process was repeated 5000 times. From these distributions of the maximum null-hypothesis difference for each subtraction, the threshold for significance was computed as the density difference corresponding to the 95th percentile of the null distribution, or $\alpha = 0.05$, brain-wise (over the whole brain), one-tailed.

Table 2
Summary counts across all brain regions

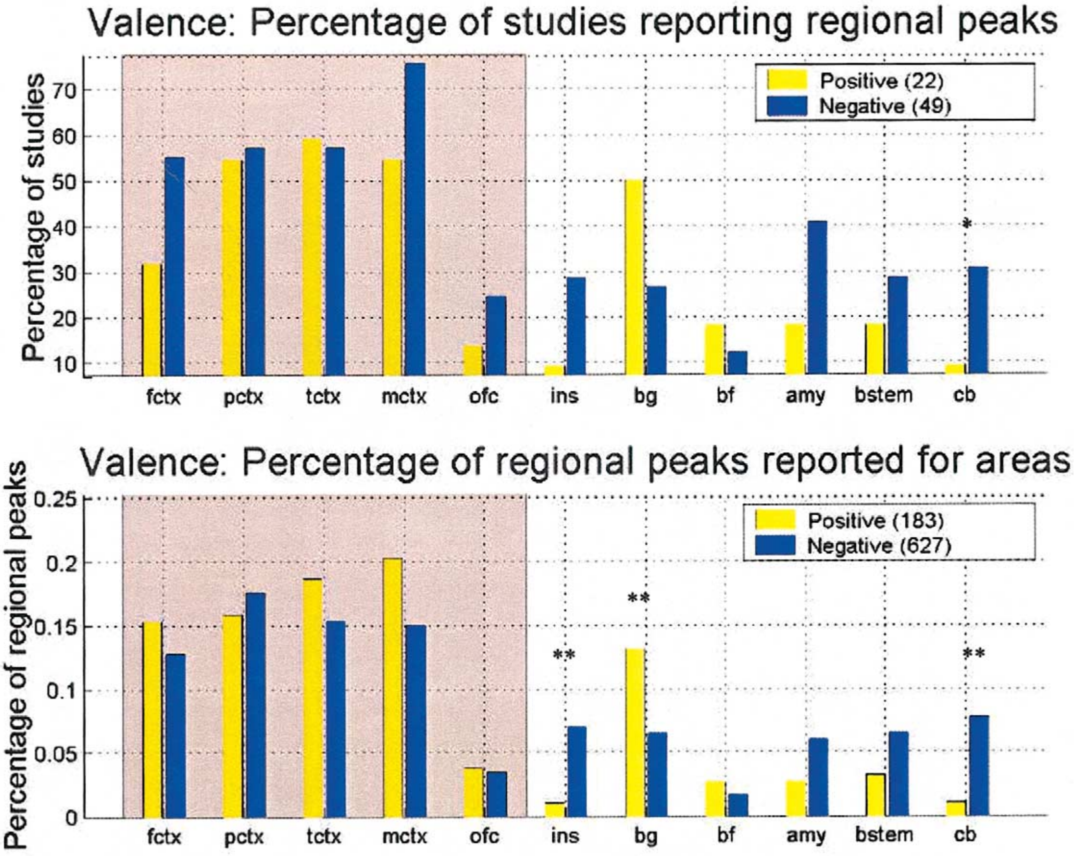
	Left	Right	*P*
Approach	103	92	0.47
Withdraw	247	227	0.38
Total	350	319	0.25
Positive	75	67	0.56
Negative	275	252	0.34
Total	350	319	0.25
Male	115	116	1.00
Female	100	84	0.27
Total	215	200	0.49

Note. Points counted as left or right were at least 6 mm from the midline. *P* values reflect two-tailed binomial test results on the minimum of left and right counts compared to the total left + right counts.

Data analysis—lateralization

To test laterality × condition interactions, we conducted binomial tests on peak counts in the left vs right hemisphere, testing left and right hemisphere peaks against the null hypothesis of even distribution across hemispheres. For overall lateralization tests that allow the direction of lateralization to vary by region, we computed a lateralization score for each condition (e.g., positive/negative) within each region by subtracting left peaks from right peaks, and summing the scores to obtain an overall lateralization score for each condition. The lateralization scores across conditions were tested for differences using χ^2 analyses, adjusting for the base-rate of peak counts in each condition.

Regional lateralization was analyzed using χ^2 and binomial tests. For each region, the total numbers of emotional activation peaks in the left and right hemispheres and in the midline were counted. All points counted as left or right were more than 6 mm from the plane dividing the hemispheres ($x = 0$), and those within 6 mm on each side of the midline were considered midline activations. Left and right counts were analyzed using a binomial test by comparing the counts to a null-hypothesis binomial distribution containing equal proportions of left and right counts. Left and right activations were compared within each condition (each category in the dimensions of *valence*, *approach/withdrawal*, and *gender*) collapsed across regions, within regions collapsed across conditions, and within each region/condition combination.



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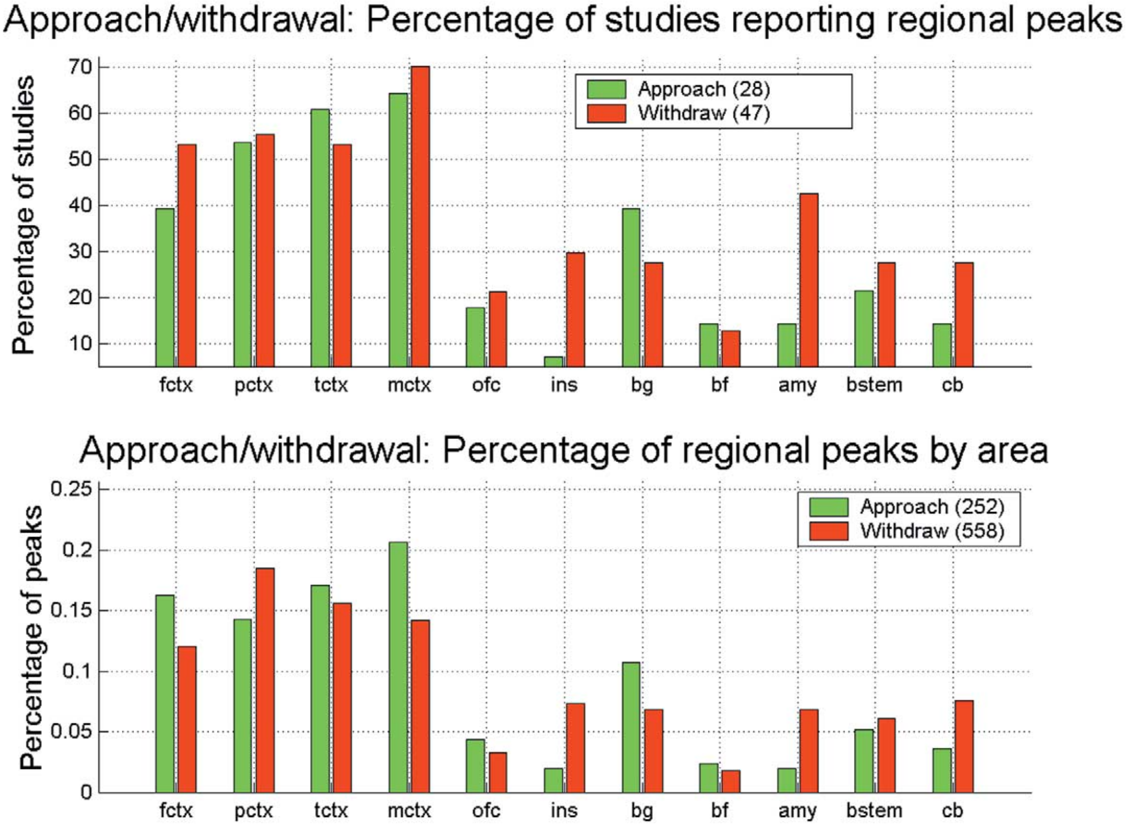

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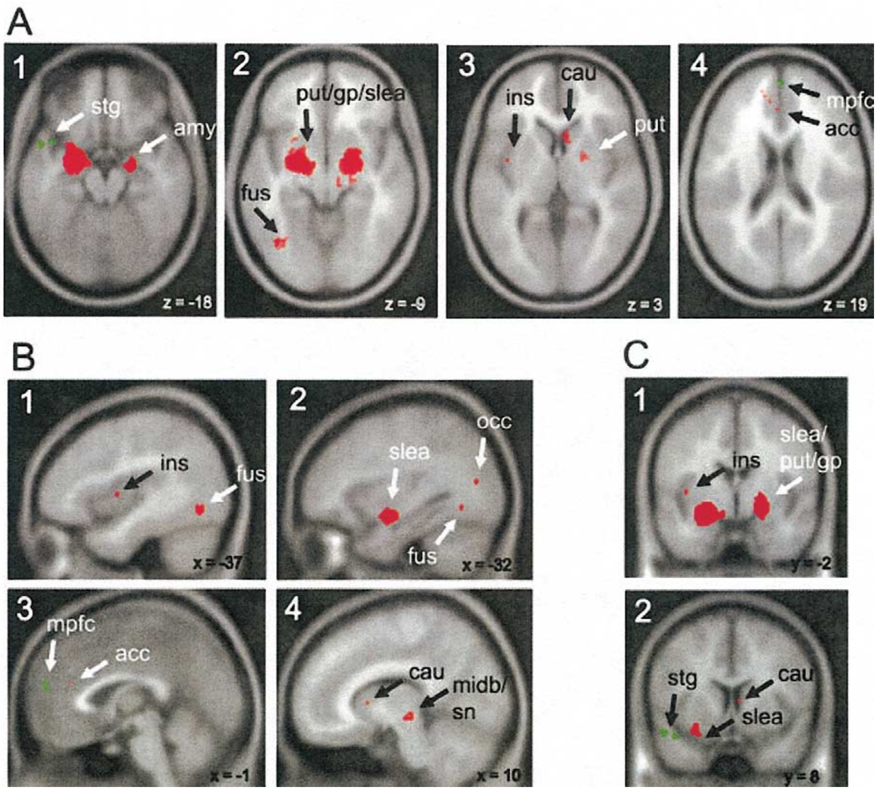
Fig. 1. Percentage of studies (top) and peaks (bottom) categorized by valence and reported region. Total counts for each valence category are in parentheses in the label. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ on test of condition within region.

Fig. 2. Percentage of studies (top) and peaks (bottom) categorized by approach/withdrawal and reported region. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ on test of condition within region.



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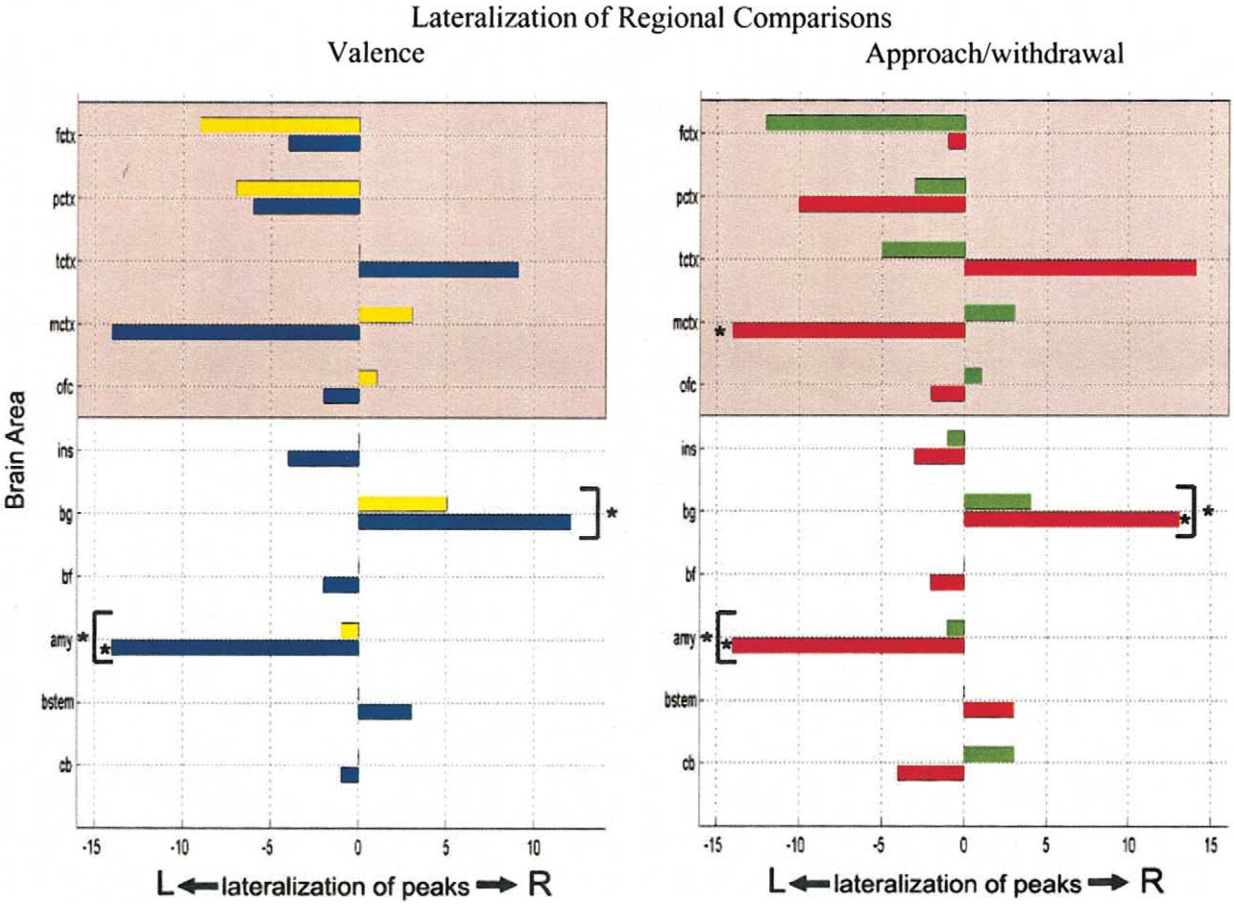

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Fig. 3. The figure shows areas where the relative density of activation foci was greater for withdrawal (red) and greater for approach (green) comparisons. Results are superimposed on the Montreal Neurologic Institute template. All suprathreshold points are significant at $P < 0.05$, brain-wise error rate. acc, anterior cingulate; amy, amygdala; cau, caudate; fus, fusiform; gp, globus pallidus; ins, insula; midb, midbrain; mpfc, medical prefrontal cortex; put, putamen; slea, sublenticular extended amygdala; sn, substantia nigra, stg, superior temporal gyrus. The left side of the brain appears on the left side of the images.

Fig. 4. Lateralization of regional peaks by valence (left) and approach/withdrawal (right) and reported region. Bars extending to the left of 0 on the abscissa indicate left lateralization, and bars extending to the right indicate right lateralization. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ on test of laterality within condition and region, or within region across conditions if marked by brackets.

Table 3
Peak counts by condition, region, and laterality

Region	Approach			Withdraw			Positive			Negative			Male			Female		
	Left	Mid	Right	Left	Mid	Right	Left	Mid	Right	Left	Mid	Right	Left	Mid	Right	Left	Mid	Right
fctx	26	1	14	32	3	31	18	1	9	40	3	36	26	1	14	18	3	13
pctx	18	3	15	51	11	41	17	2	10	52	12	46	24	3	26	11	2	6
tctx	24	0	19	36	0	50	17	0	17	43	0	52	17	0	33	18	0	21
mctx	10	29	13	28	37	14	6	22	9	32	44	18	13	17	9	11	18	8
ofc	4	1	5	9	2	7	2	1	3	11	2	9	5	1	5	2	1	1
ins	3	0	2	22	0	19	1	0	1	24	0	20	9	0	4	8	0	6
bg	10	3	14	9	7	22	8	3	13	11	7	23	4	1	12	8	9	10
bf	1	4	1	4	4	2	1	3	1	4	5	2	1	2	0	0	5	0
amy	3	0	2	26	0	12	3	0	2	26	0	12	12	0	7	8	0	4
bstem	4	5	4	11	9	14	2	2	2	13	12	16	2	1	3	8	7	7
cb	0	6	3	19	8	15	0	2	0	19	12	18	2	1	3	8	3	8
Total counts			247			555			178			624			258			232
Total lateralized			33			80			26			71			55			26

Note. Points counted as left or right were at least 6 mm from the midline. Total lateralized refers to the sum, across all regions, of the left–right imbalance for each region. This measure, calculated as the sum of the absolute value of R–L peaks for each region, denotes the degree of lateralization for a condition, irrespective of differences in the direction of lateralization among regions.

Results

Hypothesis 1. Hemispheric lateralization hypothesis: the right hemisphere is more likely to process emotions (main effect of laterality)

Hemispheric effects

No significant lateralization of counts was found for valence or approach/withdrawal when the data were collapsed across brain regions, as shown in Table 2. Nominally more activation peaks for emotional activation were reported in the left hemisphere than the right, contrary to the hypothesis, but the difference was not statistically significant. Overall, we found no support for Hypothesis 1, that the right hemisphere is more likely to process emotional material than the left hemisphere.

Hypothesis 2. Regional activations differ according to emotional valence and/or approach/withdrawal classification

Regional valence and approach/withdrawal effects

The results supported Hypotheses 2a and 2b for particular brain regions. The findings are described by region below. The ROI analysis for valence is depicted in Fig. 1 (positive vs negative) and Fig. 2 (approach vs withdrawal). Counts by condition, region, and hemisphere are shown in Table 3. Density results for approach/withdrawal are shown in Fig. 3, and χ^2 results for lateralization of regional activations are shown in bar graphs in Fig. 4.

Lateral frontal cortex. We first sought to test valence lateralization for the frontal cortex, since this region has received the most attention with respect to this hypothesis (Davidson, 1995). Approach-related activations show a trend toward left-lateralization in the lateral frontal cortex, 26 L, 14 R, $P = 0.08$, consistent with the valence lateralization hypothesis (Fig. 4). There was no significant frontal lateralization based on positive/negative valence. To test for differences in the dorsal/ventral locations of approach and withdrawal activations (suggested by Liotti and Tucker, 1995), we constructed 95% confidence volumes about the mean position of approach and withdrawal peaks in lateral frontal cortex, shown in Fig. 5. Although the mean coordinate for approach activations was dorsal to the mean for withdrawal activations in the left hemisphere ($x, y, z = [-39\ 12\ 25]$ and $[-37\ 18\ 16]$, respectively) and ventral in the right hemisphere ($x, y, z = [41\ 12\ 17]$ and $[37\ 15\ 25]$), confidence volumes overlapped for both hemispheres, indicating no significant differences in mean spatial position. Valence results were very similar to those for approach/withdrawal. The density results did not reveal any additional evidence for left/positive, right/negative lateralization in the lateral frontal cortex.

Amygdala and basal forebrain. The amygdalae were more frequently activated by withdrawal than approach, ($\chi^2 = 8.04$, $P < 0.01$ for peaks, $\chi^2 = 6.44$, $P = 0.01$ for studies), but this distinction was not significant for the positive/negative comparison. Amygdala activations were lateralized to the left, particularly for negative emotions (across conditions, 29 L, 14 R, $P < 0.05$; negative, 26 L, 12 R, $P < 0.05$; withdrawal, 26 L, 12 R, $P < 0.05$). Withdrawal-related densities were found bilaterally in the amygdala, extending into the surrounding basal forebrain, sublenticular extended amygdala (SLEA), and ventral striatum, including ventral portions of the globus pallidus and putamen (Figs. 3A, Plates 1–3, and 3C, Plates 1–2), in agreement with the χ^2 results. The significant withdrawal activation densities were centered in the superior amygdala, in the approximate area of the central nucleus, and extended into the basolateral amygdala primarily in the left hemisphere, as shown in Fig. 3C, Plate 1.

Medial prefrontal cortex. χ^2 analyses showed that medial cortex was associated with approach ($\chi^2 = 5.37$, $P < 0.05$ for peaks, $\chi^2 = 0.28$, ns for studies) overall, and that withdrawal activations were left-lateralized in the medial cortex (28 L, 14 R, $P < 0.05$; Fig. 4, right panel). Density results showed a region in the anterior medial prefrontal cortex (MPFC) with greater density of points in approach than withdrawal emotions (Fig. 3A, Plate 4). Interestingly, left rostral anterior cingulate, immediately caudal to the MPFC, showed greater density for withdrawal tasks (Figs. 3A, Plate 4, and 3B, Plate 3), in agreement with regional lateralization results in medial cortex (Fig. 4).

Basal ganglia. Across valence conditions, we found that positive emotions were more likely to activate the basal ganglia ($\chi^2 = 9.28$, $P < 0.01$ for peaks, $\chi^2 = 3.74$, $P < 0.05$ for studies; this difference was not significant for the approach/withdrawal analysis). Basal ganglia activations, collapsing across conditions, were right lateralized (approach, 10 L, 14 R; withdrawal, 9 L, 22 R, $P < 0.05$ across conditions). Density analysis (Table 4, Fig. 3A, Plate 3) showed withdrawal-related regions in right caudate and putamen. As a whole, the results suggest frequent, but nonspatially specific, positive activations throughout the basal ganglia, and focal regions in the right striatum related to withdrawal.

Cerebellum and insula. Negative emotions were more likely to activate the cerebellum ($\chi^2 = 10.85$, $P = 0.001$ for peaks, $\chi^2 = 3.86$, $P < 0.05$ for studies) and the insula ($\chi^2 = 9.28$, $P < 0.01$ for peaks, $\chi^2 = 3.30$, $P = 0.07$ for studies). For the approachwithdrawal dimension, we also found that cerebellum ($\chi^2 = 4.60$, $P < 0.05$ for peaks, $\chi^2 = 1.79$, ns for studies) and insula ($\chi^2 = 9.32$, $P < 0.01$ for peaks, $\chi^2 = 5.36$, $P < 0.05$ for studies) were associated with withdrawal. Density analysis (Table 4, Fig. 3) showed a focal withdrawal-related density in the left mid-insula (Fig. 3A, Plate 3), but no results in the cerebellum.

Temporal and occipital cortex, midbrain. Density analysis results also identified several other regions that did not appear in the χ^2 analysis. Two neighboring regions in the left superior temporal cortex were related to approach. Left fusiform gyrus, left superior occipital cortex, and the midbrain all contained regions preferential for withdrawal (Fig. 3).

Hypothesis 3. Females and males show different patterns of brain responses to emotions

Overall effects of gender

Collapsing across brain regions, 258 peaks in 22 studies were reported for men (11.9 peaks/study), and 232 peaks in 14 studies were reported for women (16.9 peaks/study). Across the whole brain, we did not find that women were more likely to show activation, $t(34) = 1.04$, $P > 0.10$.

Effects of gender on lateralization

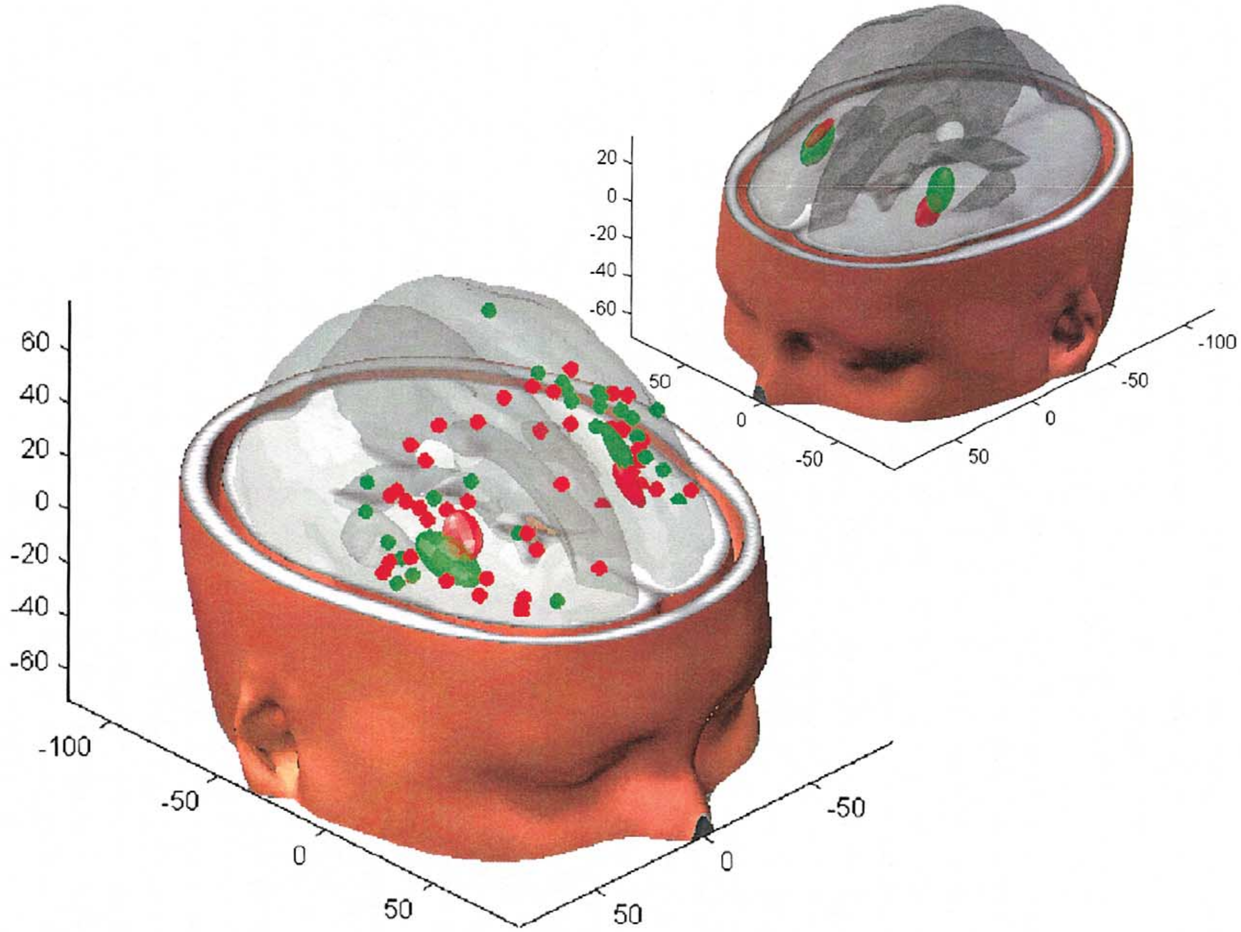
We found support for the hypothesis that men exhibit more lateralized activation of emotion than women. Collapsing across all regions and summing the absolute value of R–L peak count differences across all areas (Fig. 8), men showed more lateralized peaks (55 M, 26 W, $\chi^2 = 10.13$, $P < 0.01$, Table 3). In general, lateralization patterns were similar between males and females, except that men exhibited the pattern to a greater degree.

Regional effects of gender

Brainstem and cerebellum. Women activated brainstem ($\chi^2 = 11.50$, $P < 0.001$ for peaks, $\chi^2 = 5.64$, $P < 0.05$ for studies) and cerebellum more frequently than men ($\chi^2 = 8.58$, $P < 0.01$ for peaks, $\chi^2 = 3.90$, $P < 0.05$ for studies), as shown in Fig. 6. Density analysis showed a similar result for the brainstem, with a large, significant density region for females in the thalamus, particularly the ventral aspect of the left thalamus (Fig. 7). As in the valence comparison, the density analysis did not show differences in the cerebellum.

Amygdala. Activations from both males and females were represented approximately equally in the amygdala, and peaks for both genders were distributed fairly evenly in the right and left amygdalae, with a moderate leftward bias in both genders (Fig. 8). However, density analysis showed differentially lateralized clusters in the region of the amygdala for males and females. Males showed greater peak density in the right sublenticular area (Figs. 7B, Plate 3, and 7C, Plate 1), and females in the left sublenticular area (Fig. 7C, Plate 2). For females, the left density cluster falls in the superior amygdala and sublenticular area (Fig. 7A, Plate 1), and in the parahippocampal cortex near the temporal pole. For males, the peak density site is more posterior and superior in the sublenticular area and extends farther into the basal ganglia (Figs. 7A, Plate 2, and 7C, Plate 1). ROI analyses showed significant right lateralization in temporal cortex for men, reflecting this difference (17 L, 33 R, $P < 0.05$; Fig. 8).

Frontal cortex. Density analysis showed that females showed significantly greater peak density in the subcallosal anterior cingulate (Fig. 7B, Plate 2). Regions showing greater density for males included clusters in the left inferior frontal gyrus and anterior insula (Figs. 7A, Plates 1 and 2,



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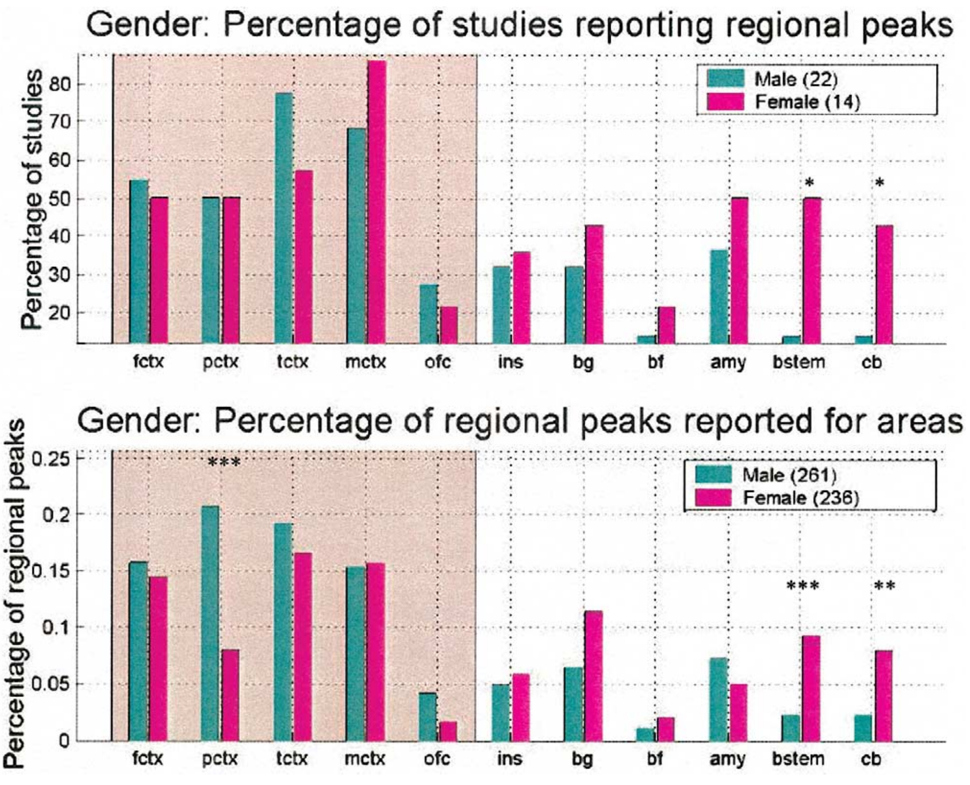

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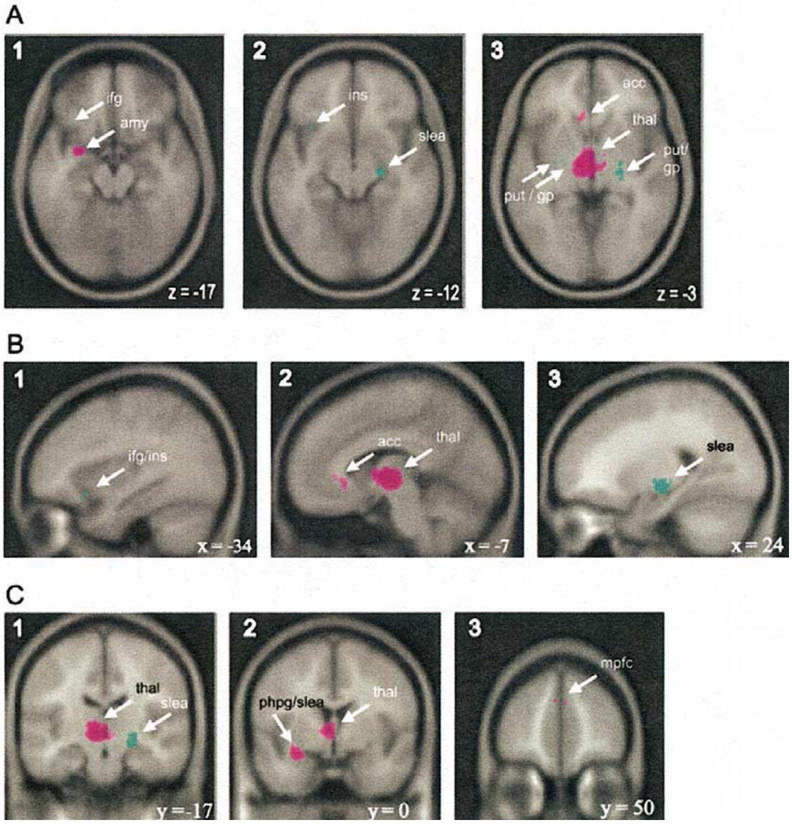
Fig. 5. Peak activations and confidence ellipsoids for approach (green) and withdrawal (red) emotions reported in the lateral frontal cortex. Overlapping confidence ellipsoids for both left and right hemisphere indicate no significant difference in the centroids for the two conditions in either hemisphere.

Fig. 6. Percentage of studies (top) and peaks (bottom) categorized by gender and reported region. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ on test of condition within region.



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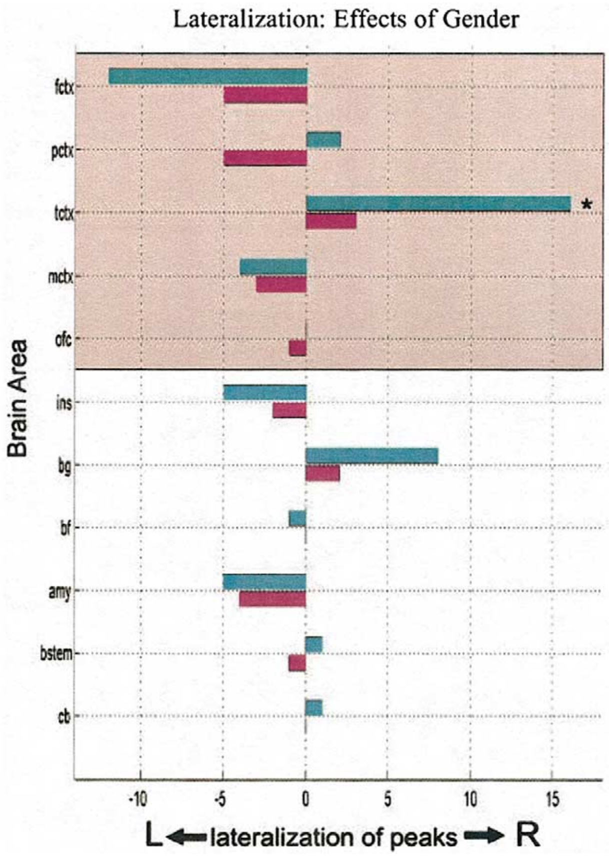

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Fig. 7. Results of density analysis for male–female (cyan) and female–male (magenta) superimposed on the Montreal Neurologic Institute template. phpg, parahippocampal gyrus; thal, thalamus; ifg, inferior frontal gyrus. See Fig. 3 legend for other region codes. The left side of the brain appears on the left side of the images.

Fig. 8. Lateralization of regional peaks by gender and reported region. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ on test of laterality within condition and region, or within region across conditions if marked by brackets.

Table 4
Density analysis results

Region	BA	x	y	z	Area	Density $\times 10^{-3}$
Approach > Withdraw						
Anterior cortex						
Anterior medial prefrontal cortex	9	1	55	16	88	1.67
		0	56	22	8	1.44
Temporal cortex						
Middle/superior temporal cortex	21/38	−52	8	−18	64	1.44
Superior temporal cortex	38	−43	9	−20	56	1.44
Withdraw < Approach						
Anterior cortex						
L. anterior medial prefrontal cortex	9/10	−14	50	17	16	2.15
	9	−12	46	20	8	2.15
	9	−10	48	24	48	2.40
	9	−8	42	20	8	2.15
Anterior cingulate cortex	24/32	−2	36	20	8	2.15
L. mid insula	13	−40	−2	3	16	2.15
Posterior cortex						
L. fusiform gyrus	19	−37	−67	−9	232	2.40
L. middle occipital gyrus	19	−32	−76	13	16	2.15
Limbic/Subcortical						
R. caudate		7	15	3	88	2.62
		6	8	6	8	2.15
R. midbrain		10	−22	−7	88	2.40
R. amygdala/basal forebrain		21	−5	−9	3416	4.53
R. globus pallidus/ventral thalamus		12	−6	0	8	2.15
L. amygdala/basal forebrain		−22	−4	−14	5376	4.77
Male > Female						
Anterior cortex						
L. inferior frontal gyrus/anterior insula	47	−34	18	−12	8	1.91
		−34	22	−16	8	1.91
Limbic/Subcortical						
L. putamen		−30	−10	−2	8	1.91
L. globus pallidus		−24	−8	−2	8	1.91
		−22	−12	−4	8	1.91
R. amygdala/basal forebrain Globus pallidus/putamen		23	−17	−7	656	2.63
Female < Male						
Anterior cortex						
Subcallosal anterior cingulate	24	−7	27	−4	168	1.91
Medial frontal cortex	9	−4	49	28	16	1.68
		3	48	26	24	1.68
		6	54	28	8	1.68
Limbic/Subcortical						
R. globus pallidus		11	−4	−2	16	1.68
L. parahippocampal gyrus/amygdala/ventral striatum		−29	0	−16	408	2.62
Thalamus (predominantly L. ventral)		−4	−10	0	5056	3.34

Note. Density clusters with significantly different densities between conditions. Coordinates are reported in MNI space. Area is the extent of the density difference in cubic millimeters, and density is the number of points per mm^3 in the significant region. Thresholds were 1.4×10^{-3} for approach–withdrawal and 2.1×10^{-3} for withdrawal–approach, estimated through Monte Carlo simulations. BA, Brodmann area.

and 7B, Plate 1) and the right putamen/globus pallidus (Fig. 7A, Plate 3).

Posterior cerebral cortex. ROI analysis showed that men activated posterior parietal/occipital cortex more frequently than women ($\chi^2 = 15.80$, $P < 0.001$ for peaks, $\chi^2 = 0$, ns for studies), as shown in Fig. 6. No corresponding results were found in the density analysis, indicating low spatial specificity of this effect.

Discussion

Whole-brain and hemisphere-level effects

Overall, the results showed that the cerebral hemisphere is too general a unit of analysis to describe data from neuroimaging. It is much more likely that specialized regions of the brain exhibit the lateralization suggested by various behavioral measures (Lane et al., 1995). Even when whole-brain-level results were significant, the direction of lateralization was region-specfic. The present results also suggest that more brain regions respect the approach/withdrawal distinction than the positive/negative one, although the two classification schemes are very similar.

The one significant "whole brain" effect found in this analysis was greater lateralization of affective response for men than women, although the direction of lateralization varied by region. One explanation is that interaction between lateralization and gender with respect to emotion may reflect a gender asymmetry for all complex brain processes. Other studies have shown a greater lateralization for men (and corresponding hemispheric symmetry for women) in affective (Cahill et al., 2001; Killgore and Yurgelun-Todd, 2001; Nopoulos and Andreasen, 1999), language (Good et al., 2001; Pizzamiglio et al., 1985; Saucier and Elias, 2001), and cognitive tasks (e.g., Benbow, 1988; Russo et al., 2000). However, other studies have failed to find gender effects on lateralization of language and other cognitive functions (Borod et al., 1998; Frost et al., 1999; Hutton, 2001; McGowan and Duka, 2000; Welsh and Elliott, 2001), indicating that gender differences in functional lateralization may be restricted to particular regions and tasks. Other effects of both valence and gender were specific to particular regions, and the discussion of them is organized by region in the text below.

Regional valence and gender effects

Medial prefrontal cortex

The finding of separate regions for approach, in the anterior medial PFC, and withdrawal, in the anterior cingulate, points to a possible dissociation of function between the medial prefrontal regions adjacent to the frontal pole and the anterior cingulate.

One function of the medial frontal cortex as a whole may be to modulate anxiety and shape behavioral responses in threatening situations. In rats, MPFC damage results in increased exploratory behavior in threatening environments and increased quinine consumption in a taste-aversion task (Sullivan and Gratton, 2002). Stimulation of the MPFC inhibits neurons in the basolateral amygdala (Rosenkranz and Grace, 2001, 2002). In humans, a negative correlation has been shown between activity measures in MPFC and amygdala (Liberzon et al., 2002).

However, our finding of withdrawal-related anterior cingulate/MPFC activation and approach-related rostral MPFC activation may indicate that there are multiple important subregions of this highly heterogeneous structure. In humans, the regions of anterior MPFC (Brodmann's area 9/10) and the anterior cingulate (BA 32/24) showing approach and withdrawal densities, respectively, have different cytoarchitectural structure (Vogt et al., 1995), although they are heavily interconnected (Devinsky et al., 1995; Vogt et al., 1995; Vogt and Pandya, 1987). Anterior cingulate function has been related to threat and negative emotion in humans (Maddock and Buonocore, 1997; Whalen et al., 1998a), as well as tasks involving cognitive conflict (MacDonald et al., 2000). The anterior MPFC/frontal pole is distinct both cytoarchitecturally and functionally, having been related to memory retrieval (Lepage et al., 2000), reward (Pochon et al., 2002), switching attention in space (Pollmann, 2001), and placebo analgesia (Petrovic et al., 2002).

More frequent activation in females than males was found in a different region of medial prefrontal cortex, the subcallosal anterior cingulate. Stimulation of this cytoarchicturally distinct area (Brodmann's area 25; Vogt et al., 1995) elicits a separation cry in monkeys (Devinsky et al., 1995) and is closely tied to the autonomic nervous system. Female-preferential activation in this area may be related to emotional expressiveness or autonomic reactions to emotional stimuli.

Amygdala and basal forebrain

The association of amygdala activation with avoidance of stimuli fits very well with the known functional anatomy of this region. Our recent meta-analysis (Phan et al., 2002) revealed a strong association between amygdala activation and fear. Specifically, we found that viewing fearful faces was the most common paradigm to produce amygdala activation: six of eight studies of conscious and unconscious perception of faces with fearful expressions showed significant amygdala response, suggesting a role for vigilance and close monitoring of environmental cues (Davis and Whalen, 2001). Since the original descriptions of nonhuman primates with temporal lobe and amygdala ablations (Kluver and Bucy, 1939), evidence has implicated the amygdala in the processing of fear-related stimuli (Weiskrantz, 1956). In rodent models, the amygdala mediates fear-conditioning (Davis and Whalen, 2001; LeDoux, 1992), and lesions of the amygdala in humans impair the recognition of fearful facial expressions (Adolphs et al., 1995; LaBar et al., 1995; Sprengelmeyer et al., 1999) and auditory cues signifying threat (Isenberg et al., 1999; Scott et al., 1997). Electrical stimulation of the amygdala produces fearful responses (Halgren et al., 1978).

However, in spite of the predominance of withdrawal-related tasks in studies reporting amygdala activation, the function(s) of the amygdala may be to perform operations, such as signaling the salience of stimuli, that are not necessarily valence-specific. Many studies reviewed here, as well as other studies not included in the meta-analysis, report amygdala activation to positive or approach-related stimuli. Some approach-related emotion paradigms that have elicited amygdala activation include viewing pleasant pictures (Hamann et al., 2002), reading positively valenced words (Hamann and Mao, 2002), and viewing happy faces (Breiter et al., 1996). Other studies have shown relationships between amygdala activation and personality traits, including dispositional pessimism (Fischer et al., 2001), affective style (Davidson and Irwin, 1999), and extraversion (Canli et al., 2001). Another set of studies has linked amygdala activation to enhanced perception of emotional material (Anderson and Phelps, 2001) and memory for emotionally salient material (Cahill et al., 1996; Hamann, 2001; McGaugh et al., 1996). One explanation that accounts for this pattern of findings is that the amygdala plays a general role in processing salience, or evaluating the relevance of stimuli to one's well being, and in reallocating cognitive resources to deal with threatening situations. This view by no means precludes the possibility that parts of the amygdala may also play other specific roles, such as mediating autonomic and behavioral responses to contextual fear cues.

Left-lateralization of amygdala function in emotion studies has been proposed by several groups, based on findings from both lesion patients and imaging studies (Anderson and Phelps, 2001; Killgore and Yurgelun-Todd, 2001; Phelps et al., 2001; Phillips et al., 2001). Morris and colleagues have proposed that stimuli processed below the level of awareness activate the right amygdala, whereas consciously processed emotional stimuli preferentially activate the left amygdala (Morris et al., 1998). The asymmetry may be attributed to more rapid decreases in right amygdala and greater right amygdala activity to neutral stimuli (Phillips et al., 2001). However, using masked presentations, presumably below the level of subjective awareness, Whalen and colleagues have found bilateral amygdala activation (Whalen et al., 1998b). The majority of studies covered in this review have used explicit, conscious presentation of stimuli, which might account for the left-sided predominance of activation. Additional work will be needed, however, to answer questions about time-course and level of awareness on lateralized function.

Recently, several groups have reported sex differences in lateralization of amygdala activations. Cahill et al. (2001) 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 (2001) found left lateralization of amygdala activity induced by happy faces for men only, and left lateralization for fearful faces in both sexes. While we did not find evidence for these effects in the amygdala proper (Fig. 8), we found female-left, male-right lateralization in regions surrounding the amygdala, in the SLEA for women and near the hippocampus for men (Fig. 7), indicating that emotion-memory circuits in the limbic system may be activated differently for men and women.

Lateral frontal cortex

We found only a trend toward left lateralization of approach activations in the frontal cortex, and a bilateral distribution of withdrawal activations. However, there are several reasons why an existing effect may not have been detected strongly in this analysis. First, we did not have an effective way of coding for the arousal levels of various tasks, and in order to make fair comparisons between conditions, such as positive and negative stimuli, the intensity of the elicited responses should be equated, as systematic effects of arousal on brain activation have been reported (Phan et al., in press; Williams et al., 2001). At least one imaging study reported that the expected lateralization of emotions appeared only when stimuli were matched for arousal (Canli et al., 1998). In addition, we did not distinguish between the perception of emotion and the experience of emotion, as it is difficult to ascertain the degree of "experience" in most studies. One issue the current results do address is the question of absolute vs relative lateralization, because the analysis reveals both the absolute lateralization for positive and negative emotions and the relative lateralization for the two (Fig. 4). In addition, left-lateralized approach activation in the temporal pole and right-lateralized withdrawal activation in the basal ganglia that are consistent with the valence lateralization hypothesis; these results may suggest potential dipole sources for EEG results showing valence-specific lateralization of transient emotion (Davidson et al., 1990) and affective disposition-related lateralized effects (Davidson and Irwin, 1999).

Basal ganglia

Our findings of significant withdrawal density clusters in right basal ganglia—and right lateralization (nonsignificantly greater for negative/withdrawal) in χ^2 analyses—are in agreement with findings on left hemisphere damage and depression (Robinson and Starkstein, 1989), which implicate basal ganglia (Morris et al., 1996) and suggest that with left hemisphere damage, the relatively overactive right hemisphere produces a predominance of negative affect. However, positive/approach emotions activated basal ganglia proportionately more frequently than negative/withdrawal emotions, suggesting that different parts of this highly heterogeneous group of structures (Parent et al., 1995) play different roles in affect. Gender differences in these effects appear to exist: females showed more frequent activation in the basal ganglia overall, but males showed more concentrated clusters of peaks in the striatum, particularly in the right hemisphere.

One potential function of the basal ganglia in emotion is programming and initiating emotion-induced behavior (Aldridge et al., 1997; Jaeger et al., 1993, 1995), although it may not be directly related to movement. In positive emotions, basal ganglia may play a pivotal role in broadening the repertoire of accessible thoughts and actions that leads to exploratory behavior and skill-building (Fredrickson, 2001), leading to activation of a number of functional loops in the basal ganglia that implement a wide range of thoughts and behaviors. In aversive situations, the basal ganglia may play a role in developing a specific action plan to deal with threat, leading to focal activation of circuits implementing more stereotyped responses.

Parieto–occipital cortex

The finding of left dorsal and ventral occipital activations (Figs. 3A, Plate 2, and 3B, Plates 1–2) shows that the patterns of activity in visual processing areas are more complex than might be predicted by behavioral research showing a left-hemifield (LVF; right hemisphere) advantage for emotional processing as a whole (e.g., Burton and Levy, 1991).

Gender differences in brainstem and cortical regions

Our analysis showed that women more frequently activate midline limbic structures, including the subcallosal anterior cingulate, thalamus, midbrain, and cerebellum, whereas males showed more activation in left inferior frontal and posterior cortex. While speculative, one possible explanation is that males may direct more attention to sensory aspects of emotional stimuli and tend to process them in terms of implications for required action, whereas females direct more attention to the feeling state engendered by emotional stimuli (Orozco and Ehlers, 1998). Another possibility is that women show greater overt response to emotion, possibly for social reasons (Grossman and Wood, 1993; Kring and Gordon, 1998). Either explanation could underlie gender differences during emotional activations and during resting cerebral glucose metabolism (Gur et al., 1995). The posterior cortex activations found more frequently in men are likely to be related to visual induction of emotion, with many of them elicited by disgusting or aversive pictures (Phan et al., 2002). Studies of brain damage have suggested that subcortical brain damage impairs subjective feeling of emotion, whereas cortical damage impairs perception of emotion (Borod et al., 1996). Imaging studies have found that female subjects have higher resting brainstem (George et al., 1996) and cingulate cortex (Gur et al., 1995) rCBF. However, neuroimaging differences between males and females do not necessarily imply behavioral or psychological differences, and we stress again that these interpretations are speculative.

Limitations of this review

While a meta-analysis can address experimental questions with statistical power greater than individual studies, certain limitations of combining different studies must be kept in mind while interpreting results. For the studies of emotion analyzed here, different techniques to elicit emotional responses are combined. “Withdrawal,” for example, includes evocative, aversive pictures (e.g., Lane et al., 1997; Lang et al., 1993; Taylor et al., 2000) as well as recall of sad experiences (e.g., Damasio et al., 2000). This review seeks to find regional specificity common to multiple techniques and methods. However, the results reported here do not invalidate findings from individual studies. One specific experimental procedure may be more robust or sensitive than another procedure intended to elicit a similar response. In addition, we did not covary or analyze differences in physiological arousal among studies; it is possible, for example, that arousal interacts with gender to produce some of the observed gender effects. Furthermore, laterality and gender effects—the main interest of this review—might vary with specific emotions, such as happiness or anger, but because of the limited number of studies in each category, we could not examine all possible interactions. One important distinction for future work is the perception of emotions in others vs the experience of emotions by the subject.

In addition, some studies used different thresholds based on a priori regions, such as the amygdala. This may account, in part, for the higher density of findings in regions such as the amygdala, and care must be taken not to overinterpret the relatively high density of peaks in this region. Differences in statistical thresholds between studies present problems in a meta-analysis of this sort; here, we have chosen to include all eligible studies, but with many more published studies to choose from, selecting studies that meet a uniform threshold might be advantageous. Finally, counting the number of reported peaks is inherently limited by the methods of peak finding and reporting. In principle, a very large activation, in extent or magnitude, may have a single high peak, and a smaller activation may have multiple local peaks. The existence of such situations would create a discrepancy between conclusions drawn from considering activation magnitude, as is often done in individual studies, and conclusions drawn from the frequency of activation across studies. To ameliorate interpretation, we have reported both peak and study counts. Although it is possible that weaker activation in an area could produce more peaks in a population of studies, we think this is highly unlikely, as there is no a priori reason why weaker activation should produce more distinct suprathreshold peaks.

Summary and conclusions

Overall, the studies reviewed here suggest that the level of anatomical specificity at which earlier theories of emotion have been framed is too coarse. We found no differences between cerebral hemispheres, as a whole, on emotional processing, and no interactions between hemisphere as a whole and valence or gender effects. When gross brain structures within hemisphere are considered, valence, gender, and lateralization effects emerge in a more complex pattern than previous theories have suggested. Left lateralization of emotion was found in some brain structures, and right lateralization in others (Figs. 4 and 8).

We found limited support for left lateralization of positive/approach emotions in the lateral frontal cortex. As a whole, our findings appear consistent with the idea, proposed by Tucker et al. (1995), that withdrawal/negative emotion-related activity is predominantly left-lateralized in the limbic system. We found left-predominant withdrawal activations in left insula, SLEA, and medial frontal cortex, although we did not find any significant right-lateralized approach/positive activations. In contrast, significant striatal activation for withdrawal was bilateral, but largely in the right caudate and putamen, in agreement with findings on lateralization and brain damage (Starkstein et al., 1987).

Brain regions that showed significant modulation by valence and gender include the medial prefrontal cortex, anterior and inferior temporal cortex, occipital cortex, and large regions of the subcortical telencephalon. Our results suggest that the cortex and nuclei of the basal telencephalon surrounding the amygdala, the sublenticular area, play important roles in emotion tasks, and many of the differences between conditions were localized to these areas rather than to the amygdala proper. In addition, all major subdivisions of the basal ganglia showed effects of emotional valence and gender, indicating that this group of structures plays an important role in processing emotional material.

As with lateralization, we found that the neuroimaging results to date suggest a more complex regional specificity of male and female activations than previously thought. Women did not show more frequent activation overall. Men tend to activate posterior sensory and association cortex, left inferior frontal cortex, and dorsal striatum more reliably than women, whereas women tend to activate medial frontal cortex, thalamus, and cerebellum more reliably. This finding could reflect differences between the genders in tendencies toward subjective feeling and sensorimotor processing of emotional stimuli, or they could reflect underlying processing differences without obvious effects on behavior. These findings provide evidence that the emotional brain is much more complex than indicated in the simple hemisphere-level predictions of the past, and highlight the usefulness of imaging studies in the generation of more specific hypotheses regarding the brain's role in emotion.

We are just beginning to understand the functions of the brain, and how brain regions interact to produce thoughts, actions, and subjective feeling states. More sophisticated analysis of imaging studies that can discern complex patterns of covariation, e.g., functional connectivity, will likely provide additional experimental leverage. The studies reviewed here, utilizing a simple subtractive approach, can still provide information about which regions are activated by particular tasks and, importantly, about the boundary conditions for involvement of a particular brain region, with consequent insight into the functional neuroanatomy of human emotion.

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